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DIAGNOSTIC CUTANEOUS REACTIONS TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY AND OF ANTIGEN PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF DIVERSE DISEASES

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THE consistent isolation by special methods of specific types of green-producing or alpha streptococci from infection atria and from tissues involved in various epidemic and nonepidemic diseases has been reported.[5,7] The inherent or acquired property of streptococci to localize and produce lesions in tissue of animals, corresponding to those chiefly involved in the spontaneously occurring disease in question, was often so pronounced as to resemble the specific pharmacological action of certain drugs or chemicals.[3,4] This tendency of streptococci to localize electively was shown to be due to the production, within the organisms themselves and free in broth cultures, of highly labile toxins or poisons which had predilection for, and specific damaging action on, the very tissues in which localization and growth occurred in the spontaneous and experimentally reproduced diseases. Similar original and corroborative studies on specificity of alpha streptococci have been reported by others, to which reference has been made in prior publications.

Evidence of specificity of streptococci as isolated in studies of various diseases was not limited to elective localization. The distribution curves of cataphoretic velocity of the streptococci varied according to the embryologic origin of the tissues chiefly involved and for which the streptococci had respective elective affinity.[6] Moreover, the different types were agglutinated, and extracts were precipitated specifically by the respective antiserums.[5,7]

Each of these procedures used for demonstrating specificity of streptococci—elective localization, agglutination and precipitation reactions, and

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cataphoretic mobility—are cumbersome, time consuming, and difficult. Special methods for their isolation and for preservation of specificity have been found necessary, and even these do not always suffice. A search, therefore, was made for simpler methods for the detection of the presence of specific types of streptococcal infections and antibody response in persons suffering from different diseases.

In agreement with the erythematous antibody-antigen reaction discovered by Foshay[1] in tularemia and with the antigen-antibody reaction described by Francis[2] in pneumonia, it was found that an immediate erythematous reaction on intradermal injection of streptococcal antibody served for the detection of specific antigen, and that a similar reaction to intradermal injection of antigen served for the detection of specific antibody in skin or blood in persons suffering from the respective type of streptococcal infection. It is the purpose of this paper to describe the methods used and report the results obtained in cutaneous tests made with natural and artificial streptococcal antibody and with antigen, and the effects of therapeutic injection of artificial antibody in persons suffering from diverse diseases associated with, or due to, green-producing or alpha streptococci.

METHODS OF STUDY

The streptococci from which natural and artificial antibody and antigen were prepared were isolated chiefly from nasopharyngeal swabbings of persons ill with diverse diseases and, as a control, from well persons remote from epidemics. For the isolation of specific types, serial dilution cultures of the NaCl-solution washings of the swabbings were made at steps of 10^{-2} or 10^{-4} in tall tubes of freshly prepared dextrose brain broth. Pure cultures of the streptococci were obtained from the end point of growth, and these were grown for only one, two, or three culture generations in this medium and then inoculated into large volumes (3,500 ml.) of freshly prepared, warm, 0.2 per cent dextrose broth. All cultures were incubated at 33° to 35° for only fourteen to twenty hours, and the growth in the large volumes of dextrose broth was harvested in the bowl of a continuous-feed centrifuge. The putty-like growth was removed from the bowl with a sterile spatula and suspended in glycerol, 2 parts, and saturated NaCl-solution, 1 part, so that each ml. of this suspension contained the growth from 500 ml. of broth, or approximately 1,000 billion streptococci. The streptococci in this suspension, owing to the hygroscopic properties of the glycerol, become dehydrated. Some remained viable for a year or two and remained antigenically specific almost indefinitely. The use of the highly favorable medium, dextrose brain broth, which affords a reduced oxygen tension, the short period of growth of the organisms, and the dense suspension were found essential for the primary isolation of specific types of alpha streptococci and for maintaining their specific properties.

Appropriate dilutions of the dense suspension of the streptococci, and not the streptococci grown indefinitely on artificial mediums, were used for

the immunization of horses, for the preparation of artificial antibody and of antigen as used in cutaneous tests and in treatment, for the preparation of vaccines and solutions of specific polysaccharides and extracts for precipitation tests, and for suspensions suitable for agglutination tests.

Ten per cent solutions of the euglobulin fraction of the serum of horses that had been immunized with the respective streptococci, and the bacteria-free supernatant of NaCl-solution suspensions containing 20 billion streptococci per ml., that had been autoclaved at 17 pounds pressure for ninety-six hours, diluted with equal parts of NaCl-solution containing 0.4 per cent phenol, were used in cutaneous tests for the detection of specific antigen.[8] The supernatant of suspensions containing 10 billion streptococci per ml., which had been heated at 70° C. for one hour, were used for the detection of specific antibody in skin or blood.

The Luer type of syringe of 0.5 ml. capacity, fitted with a 27-gauge needle, was used. Solutions of antibody and antigen considered homologous to the disease at hand in the persons to be tested, together with heterologous and control solutions, were drawn into syringes before beginning the injections. The skin was disinfected lightly with pledgets of absorbent cotton or gauze moistened with 95 per cent alcohol. Approximately 0.03 ml. of the test and control materials were injected in rapid succession, 5 cm. apart in two rows, into the skin of the volar aspect of the forearm, beginning at the bend of the elbow and proceeding towards the wrist.

The maximal area of the rapidly occurring erythema was outlined with pen and washable ink and recorded in square centimeters by superimposing circles of predetermined size on a 4 by 6 inch transparent discarded x-ray film. The solutions of antibody and antigen were kept in small rubber-capped vials, and the syringes containing the test materials were kept upright in test tubes containing enough 95 per cent alcohol to bathe the needle. They were kept in the refrigerator when not in use. The material in the syringes was not wasted after storage, but a few drops were discarded just before use to wash out any alcohol that might have diffused into the lumen of the needle. Solutions of natural and artificial antibody, when kept in the refrigerator, have been found to remain potent for as long as five and three years, respectively.

The reactions varied greatly in intensity and size, and at times were blotchy and irregular in outline. Their significance was always considered in relation to reactions or lack of reactions following injection of suitable control antibody or antigen and usually of NaCl-solution containing 0.2 per cent phenol. The erythema following injection of specific antigen occurred less often than that following injection of antibody, and was usually less intense and more transient than the reaction that followed injection of antibody. The reactions began to fade promptly. Slight edema and erythema were sometimes noted twenty-four hours later at the site of injection of the antigen. The size of reactions were usually checked by two or three observers, and large and small groups of well persons and per-

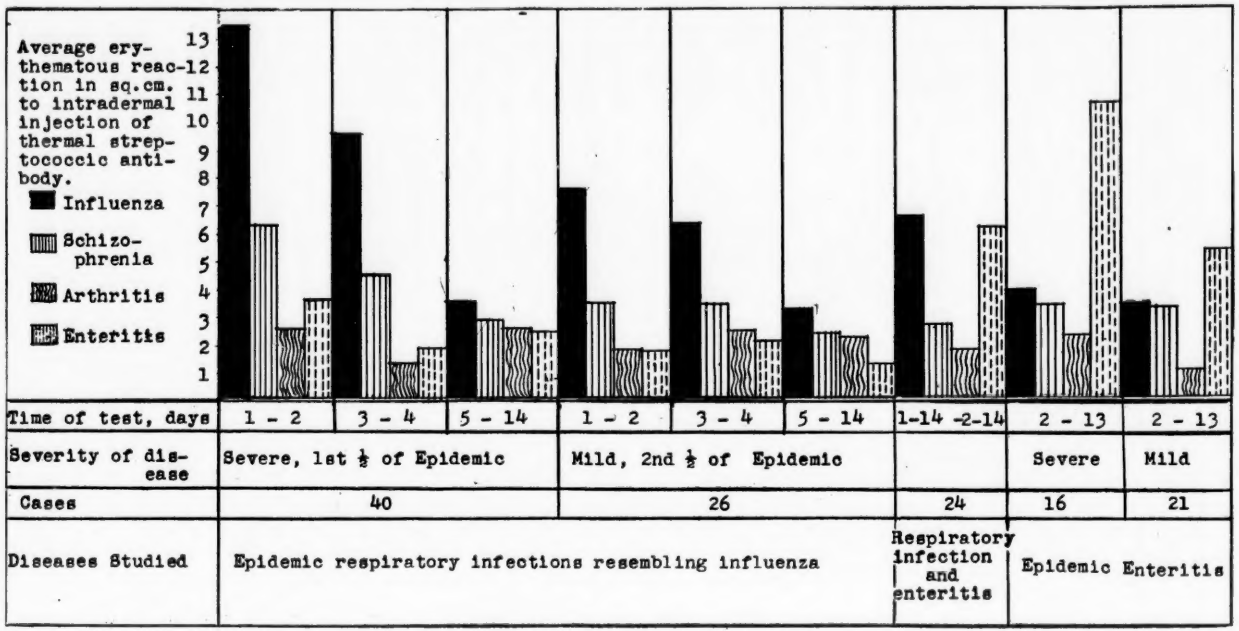

Fig. 1. Erythematous reactions to intradermal injection of thermal antibody produced from alpha streptococci isolated, respectively, in studies of epidemic respiratory infections, schizophrenia, arthritis, and epidemic enteritis.

TABLE I. ERYTHEMATOUS REACTIONS, IN PERSONS SUFFERING FROM INFLUENZA AND OTHER RESPIRATORY INFECTIONS, PERSISTENT HICCUP AND ARTHRITIS, TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE DISEASES

Groups	Reactions of intradermal injection of natural and artificial antibody prepared from streptococci isolated in studies of:						
	Natural Antibody				Artificial Antibody		
	Resp. Infections	Polio-myelitis	Encepha-litis	Arthri-tis	Resp. Infections	Encepha-litis	Arthri-tis
Influenza and other respiratory infections	256 **10.42**	46 1.76	37 2.2	45 2.3	263 **11.04**		185 2.13
Influenzal broncho-pneumonia	42 **8.90**			42 2.90	6 **11.14**	6 5.46	6 2.43
"Virus" or atypical pneumonia	17 **8.3**			17 2.05	4 **15.17**		4 3.12
Epidemic and post-operative persistent hiccup	10 *5.12*	18 4.10	42 **7.38**	28 3.12	2 *5.13*	2 **12.32**	2 1.76
Neuromyositis and fibrositis		35 3.42	35 5.10	35 **9.00**		6 4.11	6 **9.68**
Chronic infectious or rheumatoid arthritis		85 1.50	85 2.60	87 **8.12**		19 3.47	104 **9.63**

The figures above the line in each instance indicate the number of persons tested; the figures below the line indicate the average reactions in square centimeters.

sons suffering from different diseases were tested as unknowns. Reactions to several injections of the same test material ran closely parallel. In no instances did persons become sensitized or allergic following repeated intradermal or therapeutic injection of artificial antibody.

Artificial antibody used therapeutically was prepared by autoclaving NaCl-solution suspensions containing 10 billion streptococci per ml., by diluting the respective dense suspensions in glycerol-NaCl-solution 100 fold and autoclaving for three hours after adding 1.5 per cent H_2O_2.[9] The slightly opalescent solution, containing the sharply agglutinated remnants of the organisms thus obtained, was brought to pH 6.8, diluted 1 to 5 with NaCl-solution, and from 2 to 10 ml. of such dilution were injected subcutaneously or intramuscularly in treatment.

RESULTS FOLLOWING INTRADERMAL INJECTION OF ANTIBODY

The results following intradermal injection of natural and artificial antibody in persons suffering from influenza and other respiratory infections, influenzal pneumonia, "virus" or atypical pneumonia, epidemic and postoperative persistent hiccup, neuromyositis, and chronic infectious or rheumatoid arthritis, are summarized in Table I. The reactions were highly specific to both natural and artificial antibody.

TABLE II. ERYTHEMATOUS REACTIONS, IN PRISONERS AT A PENITENTIARY DURING AN EPIDEMIC OF RESPIRATORY INFECTION, TO INTRADERMAL INJECTION OF ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF RESPIRATORY AND OTHER INFECTIONS

Time of Tests	Persons Tested				Reactions (sq. cm.) to intradermal injection of artificial antibody prepared from streptococci isolated in studies of:					
	Total	Resp. Infections	Number	Per Cent	Chronic Encephalitis	Schizophrenia	Epilepsy	Ulcer of Stomach	Resp. Infections	Arthritis
Dec. 3 to 31, 1946	77	+	14	18	8.57	2.82	1.31	2.53	**13.57**	1.46
		0	63	82	13.01	4.47	2.00	4.45	2.26	1.55
Jan. 1 to 7, 1947	78	+	46	59	10.61	4.46	1.21	2.35	**10.98**	2.11
		0	32	41	10.71	2.14	.64	1.58	*5.02*	1.79
Jan. 8 to 15, 1947	160	+	66	41	10.96	5.70	2.61	3.10	**12.51**	2.47
		0	94	19	11.18	3.56	1.93	2.45	*5.73*	2.50
Jan. 16 to Feb. 23, 1947	180	+	6	9	13.41	5.77	2.08	1.08	**14.18**	2.69
		0	164	91	10.05	4.70	2.60	3.33	3.68	2.05

The results obtained in cutaneous tests made during two institutional epidemics among persons having mild symptoms of schizophrenia, one of respiratory infection and one of enteritis, are summarized graphically in Figure 1. The reactions to the respective artificial antibodies were remarkably specific, roughly proportional to the severity of the diseases in question, and became greatly less as recovery occurred. Pronounced reactions occurred to the two respective homologous antibodies, one prepared from streptococci isolated in studies of respiratory infection and one from streptococci isolated in studies of epidemic enteritis in persons who suffered from both respiratory infection and enteritis.

The results obtained at a penitentiary in prisoners during a sharp epidemic of respiratory infection are summarized in Table II. Each of four groups of persons, who were having respiratory infection when tested, reacted strongly to artificial antibody prepared from streptococci isolated in previous studies of respiratory infection, averaging 13.57, 10.98, 12.51, and 14.18 sq. cm. respectively. Two of four comparable groups that were free from symptoms of respiratory infection reacted significantly greater to the respiratory streptococcal antibody at the height of the epidemic (5.02 and 5.73 sq. cm.) than did two otherwise comparable groups before and after the height of the epidemic (2.26 and 3.68 sq. cm.). This increase during the height of the epidemic, indicating the carrier state, was apparently not due to contact infection.

The abnormally marked average reactions of this and a much larger number of prisoners to artificial antibody prepared from "neurotropic" streptococci isolated in studies of chronic encephalitis, schizophrenia, and from incorrigible prisoners, will be reported elsewhere. Suffice it to state here that intercurrent epidemic respiratory infections did not change the cutaneous reactivity to intradermal injection of two specimens of artificial antibody prepared from "neurotropic" streptococci.

TABLE III. ERYTHEMATOUS REACTIONS, IN PERSONS SUFFERING FROM POLIOMYELITIS, ENCEPHALITIS, MULTIPLE SCLEROSIS OR FROM ULCER OF THE STOMACH, TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE DISEASES

Groups	Reactions to intradermal injection of natural and artificial antibody prepared from streptococci isolated in studies of:										
	Natural Antibody					Artificial Antibody					
	Poliomyelitis	Encephalitis	Arthritis	Resp. Infection	Ulcer of Stomach	Poliomyelitis	Encephalitis	Arthritis	Ulcer of Stomach	Well Persons	Multiple Sclerosis
Acute epidemic poliomyelitis	484	268	270	53		254	15	23		254	
	8.97	3.30	2.41	3.21		**14.21**	4.21	2.45		3.09	
Poliomyelitis Contacts	337	90	304	124		277				277	
	4.35	1.80	1.26	1.73		**7.40**				2.60	
Well non-contacts in epidemic zones	437	110	86	229		188				188	
	3.64	1.30	2.46	2.07		**6.81**				1.62	
Well persons remote from poliomyelitis, encephalitis and influenza	787	325	270	340		128		201		128	
	1.27	0.77	1.48	2.23		1.80		1.85		0.89	
Epidemic encephalitis	54	138	59	91			25	20			
	3.27	**6.88**	1.80	3.06			**9.23**	2.21			
Multiple sclerosis	9	9	9	9		14	14	14			14
	5.84	*10.34*	2.54	1.48		*5.16*	*7.24*	2.88			**14.16**
Ulcer of stomach or duodenum	39	39	39		39	13	13	13	13		13
	4.0	*5.0*	4.0		**11.0**	0.83	*8.17*	0.90	**9.38**		1.23

The figures above the line in each instance indicate the number of persons tested; the figures below the line indicate the average reaction in square centimeters.

The cutaneous reaction obtained following intradermal injection of natural and artificial antibody in persons suffering from epidemic poliomyelitis and encephalitis, from multiple sclerosis or ulcer of the stomach, and in well contacts and noncontacts in epidemic zones of poliomyelitis and in well persons remote from epidemics, are summarized in Table III. The average reactions to both natural and artificial antibody were uniformly much greater in persons suffering from the disease in studies of which the streptococcus was isolated and from which the reacting antibody was prepared. Moreover, the reactions in well persons to antibody prepared from streptococci isolated in studies of poliomyelitis were proportional to the degree of exposure to poliomyelitis in epidemic zones and were minimal or absent in well persons remote from poliomyelitis.

The average cutaneous reactions obtained in persons suffering from idiopathic epilepsy, schizophrenia, chronic infectious arthritis, involutional psychosis, and dementia paralytica, tested in parallel with natural and

TABLE IV. ERYTHEMATOUS REACTIONS, IN PERSONS SUFFERING FROM DISEASES OF THE NERVOUS SYSTEM OR FROM ARTHRITIS, TO INTRADERMAL INJECTION OF NATURAL AND ARTIFICIAL ANTIBODY PREPARED FROM STREPTOCOCCI ISOLATED IN STUDIES OF THE RESPECTIVE OR RELATED DISEASES

Groups	Persons Tested	Reactions (sq. cm.) to intradermal injections of natural and artificial antibody prepared from streptococci isolated in studies of:					
		Natural Antibody			Artificial Antibody		
		Epilepsy	Schizophrenia	Arthritis	Epilepsy	Schizophrenia	Arthritis
Idiopathic Epilepsy	77	**8.27**	3.42	2.10	**9.60**	5.21	2.50
Schisophrenia	89	3.51	**5.66**	1.42	1.42	**7.53**	1.93
Chronic infectious arthritis	8	2.89	2.48	**6.06**	2.06	1.18	**4.74**
Involutional psychosis	7	2.11	**3.44**	2.10	2.74	**5.45**	1.47
Dementia Paralytica:							
Without Convulsions	24	2.18	1.82	0.87	1.90	1.75	0.89
With convulsions	6	**5.79**	2.45	1.35	**6.87**	3.65	2.29

artificial antibody, are summarized in Table IV. A consistently high degree of specificity was obtained with both types of antibody, including a strikingly greater average reaction to antibody prepared from streptococci isolated in studies of epilepsy in persons suffering from dementia paralytica having convulsions, than occurred in persons having dementia paralytica without convulsions. The reactions were uniformly minimal to all antibodies in the uncomplicated group of dementia paralytica, and to heterologous antibody in the groups which reacted specifically to the homologous antibody. Moreover, cross reactions were relatively greater in persons suffering from epilepsy or schizophrenia to both types of antibody prepared, respectively, from the more closely related streptococci isolated in studies of epilepsy and schizophrenia, than to antibody prepared from the streptococci isolated in studies of arthritis.

RESULTS FOLLOWING THERAPEUTIC INJECTION OF ARTIFICIAL ANTIBODY

The presence of abundant specific antigen and minimal specific antibody in skin or blood of persons in the early stages of respiratory infections, the gradual diminution of antigen, and the increase of antibody with time during the natural course of the disease and as recovery ensued, are shown graphically in Figure 2.

The effects of therapeutic injection of artificial antibody on the antigen and antibody content of skin or blood in persons suffering from influenza or other respiratory infections are shown graphically in Figure 3. The decrease in specific antigen, as shown by intradermal injection of artificial antibody prepared from streptococci isolated in studies of influenza and other respiratory infections, and the increase in antibody, as shown on intradermal injection of the corresponding antigen following therapeutic injection of specific artificial antibody, were greater in twelve and six hours, respectively, than occurred in six to nine or more days during

the natural course of the disease (Fig. 2). There was usually a corresponding improvement in symptoms, especially in the early stages of the disease as antigen was sharply reduced and antibody abruptly increased.

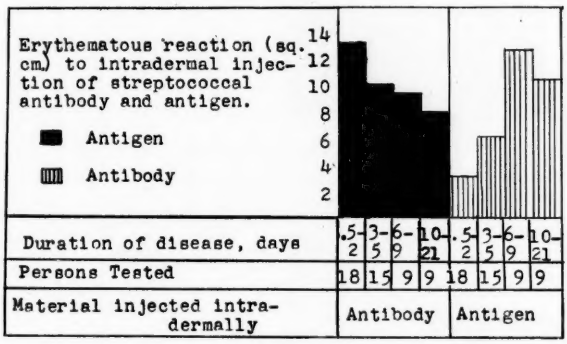

Fig. 2. Erythematous reactions, in persons suffering from epidemic respiratory infections, to intradermal injection of antibody and antigen prepared *in vitro* from streptococci isolated in studies of respiratory infections, according to the duration of the disease.

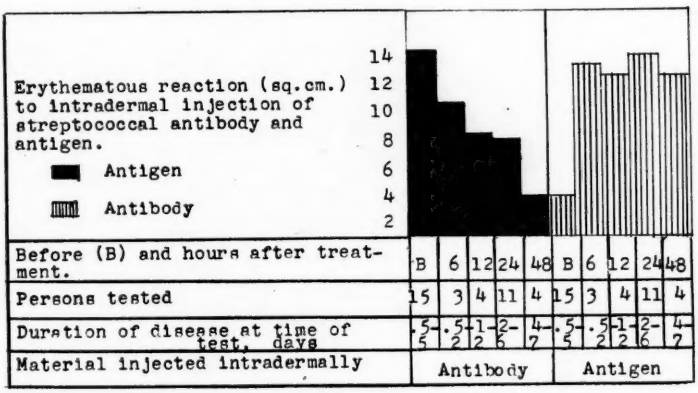

Fig. 3. Erythematous reactions, in persons suffering from influenza or other respiratory infections, to intradermal injection of antibody and antigen prepared *in vitro* from streptococci isolated in studies of epidemic respiratory infections, before and after therapeutic injection of homologous streptococcal antibody.

The effects of therapeutic injection of artificial antibody prepared from streptococci isolated in studies of poliomyelitis on the content of specific antigen and antibody in the skin or blood of persons suffering from epidemic poliomyelitis, are summarized graphically in Figure 4. A striking reduction in antigen and an increase in antibody occurred in three hours and persisted for forty-eight hours following one therapeutic injection per

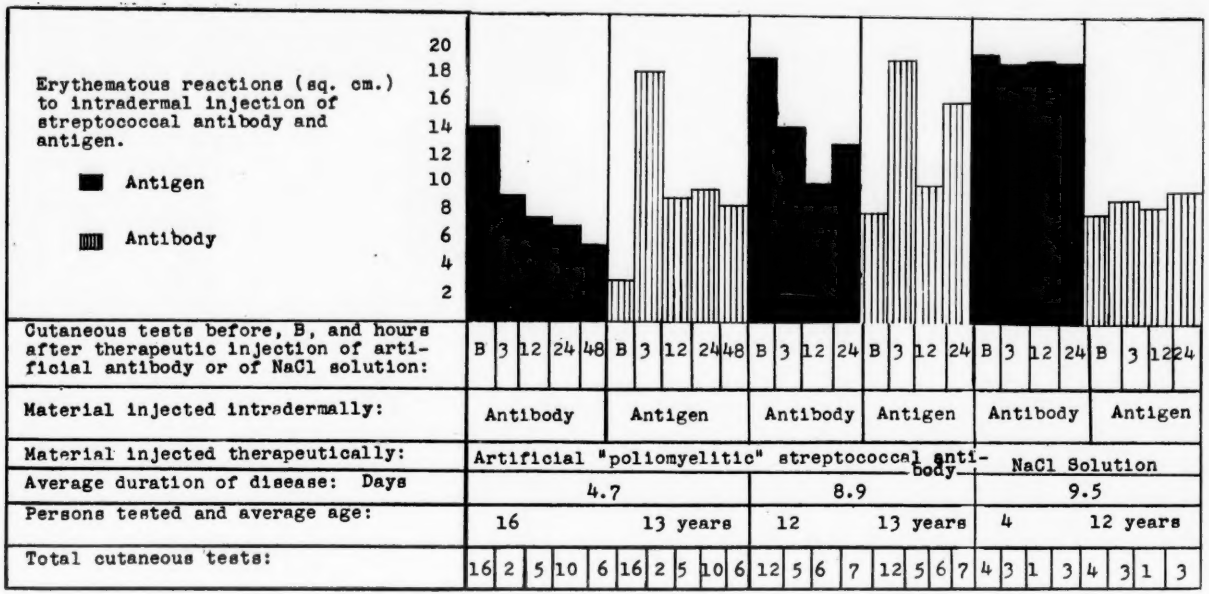

Fig. 4. Erythematous reactions, in persons suffering from epidemic poliomyelitis, to intradermal injection of antibody and antigen prepared from streptococci isolated in studies of poliomyelitis, according to the duration of the disease and therapeutic intramuscular injection of artificial antibody.

person of antibody in the group of sixteen persons in the early stages of the disease. A moderate decrease in antigen and increase in antibody occurred in the group of twelve persons in the later stages of the disease, and no change in antigen and antibody occurred in the four control persons having poliomyelitis who received "therapeutic" injections of NaCl-solution.

COMMENTS AND SUMMARY

The results of cutaneous tests in persons suffering from widely different epidemic and nonepidemic diseases, made with natural and artificial antibody and with antigen prepared from green-producing or alpha streptococci isolated in studies of persons suffering from the respective diseases and of well controls remote from epidemics, are reported.

The reactions to intradermal injection of natural antibody prepared in horses and artificial antibody prepared *in vitro* with the respective streptococci, indicating specific antigen in skin or blood and, hence, corresponding specific types of streptococcal infections, ran closely parallel. The reactions were usually proportional to the severity of respective symptoms, fairly constant in chronic disease, greatest in the early stages of acute disease, and gradually became less pronounced and finally disappeared after recovery.

Reactions to intradermal injection of antigen, indicating specific antibody in skin or blood, were often slight or absent at the onset of acute respiratory infections and epidemic poliomyelitis, but gradually increased in size as recovery occurred, and then disappeared usually as antigen also disappeared.

There was a great difference in the length of time that specific antigen was demonstrable in skin or blood in the natural course of different acute diseases. The reaction indicating specific streptococcal antigen, in acute respiratory infections followed by a transient immunity, usually disappeared in two weeks, whereas in epidemic poliomyelitis, followed by an enduring immunity, the reaction usually persisted for six or eight weeks. The erythematous reactions are not considered diagnostic of disease but rather diagnostic of the presence in skin or blood of respective specific streptococcal antigen and antibody and, hence, of specific types of streptococcal infections.

The reactions obtained on intradermal injection of natural and artificial streptococcal antibody or of antigen are almost certainly not allergic or urticarial in character, nor are they due to histamine. Wheal and pseudopodia formation and itching, characteristic of allergic and histaminic reactions, almost never occurred.

Reactions to antibody in persons suffering from the different diseases, and who reacted most strongly to homologous antibody, were relatively greater to antibody prepared from streptococci isolated from persons suffering from more closely related diseases than to antibody prepared from

streptococci isolated from persons suffering from more distantly related diseases. Reactions in persons ill with various diseases were minimal to antibody prepared from streptococci isolated from well persons remote from epidemics. Morover, reactions in well persons and persons ill with noninfectious diseases remote from epidemics were slight or entirely negative. Reactions to control NaCl-solution, to which 0.2 per cent phenol had been added after autoclaving, were slight or negative alike in ill and well persons.

Therapeutic injection of natural, and especially of artificial, antibody caused a greater reduction in antigen and a great increase in antibody in the course of hours than occurred in the natural course of acute disease during several to many days. With striking reduction of antigen and increase of antibody following therapeutic injection of artificial antibody, there was usually a corresponding clinical improvement and, in the very early stages of respiratory infection and poliomyelitis, abrupt disappearance of symptoms.

The cutaneous tests which have been developed and reported herewith are considered of importance because they are strictly objective, easily performed and controlled, and because the information obtained is in such strict accord with the demonstration, by animal inoculation, serologic and cataphoretic methods, of the presence of specific types of alpha streptococci in the diseases studied.

The supernatant solutions are designated as artificial or thermal antibody because they were prepared *in vitro* and because they agglutinated the respective streptococci in high dilution, hastened the destruction of streptococci on intraperitoneal injection in animals, caused a prompt reduction in antigen and increase in antibody on therapeutic injection, and had apparent curative action in the treatment of persons suffering from streptococcal infections homologous to the streptococcus from which the antibody injected was prepared.

Acknowledgment of the co-operation of the many attending physicians and nurses, of hospital superintendents and health officers, which made these studies possible, is hereby made.

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TRIMETON IN THE TREATMENT OF ALLERGIC DISEASES

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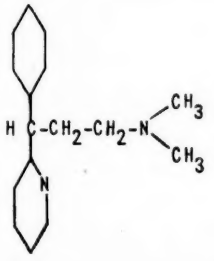
HAVING given a clinical trial to practically all of the antihistaminic agents since Benadryl was first introduced, we undertook the past year clinical observations with Trimeton to determine whether it had certain advantages over antihistaminic agents previously introduced. With the report of this small series, it is obvious that for statistical purposes it is inadequate. However, a close personal study was made of each of these cases, and the patient was told that the drug was prescribed to give symptomatic relief.

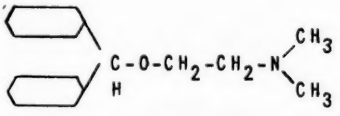
Trimeton was employed as an adjunct in allergic management and the majority were receiving concomitant immunization measures. The agent was administered only to those where allergic management proved inadequate or where insufficient time had elapsed before the pollen season to adequately control symptoms.

Although Trimeton was distributed to a considerable larger number of patients, only 125 could be properly tabulated for various reasons. An attempt was made to exclude those who exhibited evidence of secondary infection. The ages of the patients ranged from eight to seventy-four years.

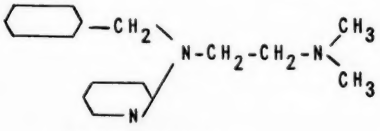
Trimeton (brand of Prophenpyridamine) has the empiric formula $C_{16}H_{20}N_2$, molecular weight 240, with a structural formula as shown below.



It is insoluble in water but soluble in organic solvents and in dilute acids such as hydrochloride acid, forming the hydrochloride. The relationship of Trimeton with Benadryl and Pyribenzamine is shown in the respective structural formulae:



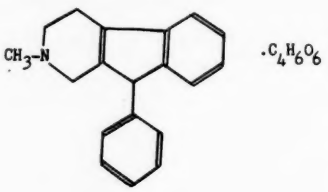
BENADRYL



PYRIBENZAMINE

Trimeton-1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane was supplied through the courtesy of the Schering Corporation, Bloomfield, New Jersey.

Thephorin belongs to a different class of compounds and has a structural formula as follows:



Thephorin

When comparing the antagonistic action against the toxic effects characteristic of histamine in animals, Trimeton showed greater activity with equal dosage. Incidentally, Trimeton shows antispasmodic activity, as measured by its ability to produce relaxation in isolated rabbit gut which has been induced into spasm by barium chloride or by carbamylcholine. The comparison of the antihistaminic action of Trimeton, Benadryl, and Pyribenzamine is quoted by Brown.[2]

Trimeton is available in 25 mg. tablets, scored. It was found that this dose three times daily was usually sufficient for the average adult, and that one-quarter to one-half a tablet would suffice for children according to age. The action of the compound commences in fifteen minutes to one hour and lasts four to six hours. Conclusions were based on questioning the patient within one or two days following the onset of treatment. Instructions were given to take the drug only when symptoms presented themselves.

At the onset, difficulty was encountered when comparing the reports of patients who had previously taken other antihistaminic agents. Syndromes which were considered allergic only were treated in this series.

Of the 125 patients which were tabulated, eighty-nine of them manifested respiratory allergy in some form, and of the eighty-nine, thirty-three were cases of pollenosis, eighteen were perennial nonseasonal allergic rhinitis, twenty-nine were bronchial asthma, four of whom had exacerbations during the pollinating season, and nine cases had a mixed syndrome of asthma and hay fever. Of the 125 patients, thirteen of them had simple urticaria, and one had angioneurotic edema. Of this series there were four with gastrointestinal allergy. There were seven cases of allergic headaches, including migraine. Six patients had atopic dermatitis, and two had contact dermatitis. Two patients of the series had general pruritus, and one patient had Ménière's disease.

Results were classified as "good," "fair," and "poor." The patients with good results had complete, or almost complete freedom from symptoms. Those with fair or moderate relief were those whose results were con-

sidered satisfactory in the majority of patients, and those with poor results were those who obtained no relief whatsoever.

Of the thirty-three patients with pollenosis, twenty-five had good results, six had fair results, and two had no results at all. The total improved, therefore, of the pollenosis group was about 90 per cent.

Of the eighteen patients with perennial allergic rhinitis, five obtained good results, four were fair, and nine obtained no relief.

Of the total of thirty-eight asthmatics, nine of whom had asthma and hay fever, six obtained good results, four obtained fair results, and twenty-eight showed poor results.

Of the thirteen patients with simple urticaria, six obtained good results, three had fair results, and four showed poor results.

One case of angioneurotic edema showed good results, although during her attack she was also taking vitamin K. This patient is still on Trimeton and with no recurrence, although recurrent attacks have been fairly frequent.

Of the four patients with gastrointestinal allergy, one obtained moderate relief from cramps, but the others obtained no relief.

Of the seven cases of allergic headaches, including migraine, six with moderately severe and very severe symptoms showed relief to date, but the time has been too brief to determine how many will show permanent relief. One patient obtained no relief.

Of the six cases of atopic dermatitis, the symptomatic relief of the pruritus was good in three, fair in two, and poor in one.

Of the two patients with contact dermatitis, no relief was obtained.

Of the two patients with general pruritus, one achieved good results, and one had fair results.

One patient with Ménière's disease obtained fair results with relief of the tinnitus and considerable relief of the vertigo. By taking 25 mg. of Trimeton three times a day, the patient could avoid this syndrome when subsequently exposed to the offending agent, tobacco.

Side Effects.—One patient with a perennial allergic rhinitis complained of nausea, which disappeared on withdrawal of the agent and recurred upon resuming treatment. One patient developed abdominal pains and vertigo. Another patient with severe hay fever over a period of several years, who had not received any immunization measures, obtained good relief until the height of the hay fever season, when she developed asthma for the first time. Whether this can be attributed to a shift in the sensitized or "shock organ" remains to be determined.

SUMMARY

When comparing the results of Trimeton with the previous observations from the older antihistaminic agents, it has been shown to give temporary symptomatic relief, particularly in patients suffering from pollenosis.

Ninety per cent of the hay fever cases due to pollen obtained good or fair relief with no side reactions. This slightly exceeds the percentages of the older antihistaminic agents such as Pyribenzamine, as reported by Arbesman and his co-workers,[1] and Feinberg and Friedlander.[3]

Comparing the results of Trimeton with those of Waldbott[5] for Neohetramine for perennial allergic rhinitis, hay fever, and urticaria, they were favorable, if not superior. According to Frank's observations[4] for Thephorin, a greater percentage of his nonseasonal rhinitis and urticaria cases were benefited; although when compared with our observations of Trimeton, a greater percentage of our pollenosis cases were benefited. Side effects, when compared with the other antihistaminic agents studied, were comparatively rare, which is a distinct advantage. Side effects, however, must be expected in varying degrees from any of the antihistaminic agents so far introduced.

The most beneficial effects were obtained when used in conjunction with immunization measures and when preventing systemic reactions with high dosage of pollen or the inhalant extracts by administering a 25 mg. tablet about a half-hour before the antigen injection. This procedure would allow increasing the maximum dose of the antigen within tolerance, than when taking the pollen extracts alone.

Trimeton is a valuable adjunct in proper allergic management. Its greatest value is in the treatment of pollen hay fever and hives, and it appears somewhat superior in the small series observed.

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ENVIRONMENTAL EXCITANTS OF IDIOBLAPTIC ALLERGY (INHALANTS)

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THE subject of this report has received some consideration in the earlier publications upon idioblapsis, especially in the paper entitled "Sensitivity to Cigarette Smoke"[1] and in a short section of the second edition of my monograph[2] (p. 55).

The environmental air-borne excitants of idioblaptic allergy have been found to cause important symptoms (epileptic seizures, hypertension and others); they sometimes interfere seriously with the interpretations of the pulse-dietary record, and they are often difficult to identify, sometimes even eluding the search for them entirely. These facts, together with the recently increased occurrence of illustrative cases in my experience, have made the publication of the latter seem worth while.

CASE REPORTS

Case 1.—The case of A. F. C. has been difficult and instructive, because of the number of the inhalant allergens that affect him, the variety and seriousness of his allergic symptoms and the length of time that was needed—on account of the continual exposure to some of the inhalants—to identify all of his food allergens. Perhaps the clinical material obtained from the long observation of this patient can be most usefully analyzed with reference to his most important symptom: allergic ("essential") hypertension.

Throughout most of his life this man had suffered severe allergic symptoms (migraine, heartburn—sometimes incapacitating—dizziness, tormenting extra systoles and others), but previous to the age of sixty-six his systolic blood pressure had usually ranged between 108 and 112. At about sixty-six and one-half years of age, December, 1941, a maximal pressure of 134/88 followed the ingestion of potato, and promptly after avoidance of the potato the pressure fell to a minimum of 100/70. Soon after he had submitted, in May, 1942, to sympathectomy (right side only) he abandoned all dietary restrictions for a short time, and two months after the operation a pressure of 154/84 was recorded. In November, 1943, the pressure stood once at 190/106. The highest systolic pressure observed in this patient has been 202, the highest diastolic 122. In 1944 after the main food allergens had been identified and eliminated from his diet, his average pressure through sixteen days (one test daily) was 137/74.7, (highest systolic 158, highest diastolic 80). He does not smoke and his sensitivity to tobacco smoke was first observed by accident after a long drive with a cigar smoker in a closed automobile. At one and one-half, three and one-fourth and four and one-half hours after the exposure the diastolic pressure readings were 96, 90 and 100, as compared with 74 and 78 on the two previous days and 86 and 78 on the two following days. After the exposure and before the next meal there was also anorexia and near-nausea. No food allergen came in question.

In 1945, notwithstanding avoidance of the major food allergens and efforts to avoid tobacco smoke, the hypertension advanced. Table I shows the pressure recorded practically daily between August 18 and September 18, 1945. The average 147.6/91.6 is higher than it had been in the previous year. In the spring of 1946 house dust became suspect, and dust-proof covers were placed on all bedding

TABLE I. BLOOD PRESSURE OF PATIENT A.F.C. TAKEN DAILY FROM AUGUST 18 TO SEPTEMBER 18, 1945. AVERAGE 147.6/91.6

140/90	150/90	150/90	150/94	150/96	146/90	150/96
150/92	144/96	150/94	148/90	130/96	144/96	158/98
150/90	152/96	150/90	152/94	152/90	152/96	144/88
152/96	148/86	140/80	142/84	140/86	140/86	160/96
150/96	140/88					

Gas range moved to semidetached kitchen October 5, 1945.

TABLE II. BLOOD PRESSURE OF PATIENT A.F.C. TAKEN ALMOST DAILY FROM MARCH 29 TO APRIL 29, 1946. AVERAGE 161/89

148/86	168/94	148/84	164/86	164/84	174/96
160/90	170/98	156/84	158/86	162/84	152/78
162/90	178/96	158/86	158/90	160/88	184/90
152/86	144/86	162/90	146/82	170/96	160/90
162/86	166/98	158/94	160/90		

Dust-proofing March 28, 1946

and most of the upholstered furniture. Nevertheless, the pressure increased somewhat, averaging 161/89 (Table II). At that time milk and cereal had not yet been recognized as residual allergens, but exposure to suspected kitchen range gas had been greatly minimized by building a semidetached kitchen. In the fall of 1946 after the cereals had been eliminated and the patient had been proved to be nonsensitive to pea, bean, peanut and onion, and having tried to lessen the exposure to dust by having him for the greater part live and sleep in the partly closed-off sun porch, the average pressure was found definitely lower in the period November 5 to December 10 (Table III).

It was not possible to judge how much of this improvement was due to elimination of the food allergens and how much to the modest measure of dust avoidance, but a prolonged stay (half-hour or more) in the house was regularly followed at once by chest oppression and dry mouth, and on the day following the periodic vacuum cleaning there was often diarrhea. It was these recurring sequences that led me at last to investigate the existing devices for the clearing of dust from the air of human habitations. There were three different types of these, all of which are efficient for their several special purposes.

The first is the familiar filter-box designed for installation in a window during the pollen seasons for the purpose of drawing pollen-free air into the room, and, through the positive air pressure thus maintained, preventing to some extent the entry of pollen-laden air through other avenues. The other two devices are much more expensive.

One of these is a system of ducts carrying air to and from the different rooms and passing it under pressure through "fiber-glas" filters and generally through water, these being connected with the central heating body.

The third device consists essentially of a set of electrically charged plates upon which are deposited practically all dust particles that are in the air passing over them. The instrument may be placed in any convenient situation in living or sleeping rooms.

It seemed to me that for my purpose a fourth type of instrument should be satisfactory and might be manufactured at a cost within the means of most persons needing it. Essentially the device consists of two "fiber-glas" filters set close together in slots in a metal housing in front of an exhaust-fan. The fan should deliver about 1,000 cubic feet of filtered air per minute. The instrument is easily portable.

When such a filter was set in motion, January 8, 1947, in the living room of A.F.C., his blood pressure in the sun porch stood at 154/90. Two hours later the odor of the lubricating oil was noticeable in the bathroom on the floor above, indicating effective circulation of the filtered air through the house. From that time the patient has lived continually in the house. The forty-eight blood pressure

TABLE III. BLOOD PRESSURES OF PATIENT A.F.C. TAKEN ALMOST DAILY FROM NOVEMBER 5 TO DECEMBER 10, 1946. AVERAGE 149/81.7

152/94	160/94	144/82	170/94	164/68	126/72
160/90	142/74	148/80	128/70	150/90	140/80
150/90	150/88	146/74	148/72	140/80	140/76
144/86	144/72	154/80	150/70	170/90	150/84
160/84	160/86	160/82	146/80	140/70	144/80

Stopped eating molasses, November 2, and stopped eating all cereals November 4. Living mostly on sunporch.

TABLE IV. BLOOD PRESSURE OF PATIENT A.F.C. TAKEN AT SEVERAL DAY INTERVALS FROM JANUARY 9 TO MAY 15, 1947. AVERAGE 142.5/76

140/78	132/74	142/80	126/72	140/74	142/74	140/72	142/76
144/78	134/76	132/76	150/76	148/76	132/68	138/68	150/76
144/76	146/76	146/74	159/70	154/82	150/82	146/74	134/74
150/72	156/80	140/70	156/78	140/70	150/72	144/80	138/68
136/70	154/88	146/82	142/74	138/70	164/96	132/74	146/80
136/72	144/82	132/78	160/82	140/70	128/68	136/78	132/68

Air filter started January 8, 1947. Living in house from January 8, 1947.

readings observed from January 9 to May 15, 1947, are shown in Table IV. These readings include all those taken after exposure to tobacco smoke, unavoidable dust and other inhalants.

House dust causes other allergic symptoms in this patient. Conjunctival smarting and tearing of long standing ceased soon after the air filter began to function, and have recurred only upon occasional later exposures to dust. Chest oppression and diarrhea have been mentioned. Neuralgic pain is an uncommon symptom, although it regularly follows exposure to paint fumes and cement dust.

A practically experimental clinical test of the patient's nonreaginic sensitivity to dust was made on January 30, 1947. At 8:30, one hour after an allergen-free meal, with the pulse at 72, he stood for twenty minutes before the functioning filter. The fan had throughout the preceding three weeks been sucking air through the filters from the front; and the electrician had just reversed the motor so that it was now blowing the air through the filters from behind, which favored a loosening of the recently deposited dust from the anterior surface of the front filter. At 8:50 the patient noticed chest discomfort, and his pulse had increased to 78 (filter was stopped). At 9:00 the chest discomfort was marked; there were extrasystoles, and the pulse stood at 82. At 9:10 the pulse was 74, and at 9:40 it had dropped to 66 and the chest discomfort had diminished. The expected diarrhea occurred on the following day. The somewhat elevated systolic pressure of 150 observed at 10:00 is not significant because the pressure had not been measured previous to the test.

Case 2.—In the past year I have had opportunity to study three hypertensive patients *none of whom was found nonreaginically allergic to any food.* As in the similar instances with other symptomatology, avoidance of such common nondietary excitants as tobacco, perfumed cosmetics, soaps, dentrifices and the like, and soap powders was advised.

One of the three patients refused to complicate his living with such restrictions and withdrew. The other two observed the precautions and also covered mattresses and pillow cushions, et cetera, with dust-proof covers. The systolic pressure on one of these (A.H.) had never been below 260 under the observation of her physician, Dr. John Dickson of Bogota, New Jersey, and at her first two visits to my office it registered above 300. The diastolic pressure was 130 and 120, respectively; Dr. Dickson had found it about 130. She had had a slight cerebral hemorrhage in July, 1945.

The first week of the pulse-dietary survey with a varied diet had revealed no food that caused a distinct and specific tachycardia. However, the variations of the maximal daily rate 70 to 78 indicated some allergenic influences. Moreover, it was noted that the before-rising count was usually higher than the retiring count.

After the dust-proofing of the bedding on April 11 the pulse-rate before rising was always slower than before retiring.

April	*5*	*6*	*7*	*8*	*9*	*10*	*11**	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Before rising	—	68	64	72	68	66	64	56	62	56	62	64	54	60
Retiring		60	—	68	64	56	60	68	72	68	66	62	64	70

*Dust-proof covers on bedding.

On May 4 the blood pressure stood at 194/118, and at that time the patient was urged to obtain an air filter. Another sign of the favorable effect of the dust precautions was the fact that the daily maximal pulse rate on each of the previous twelve days (excepting two days when it was 68) had been 70. On the date of this writing (August 29, 1947) the patient reports that she has still been unable to obtain the needed air filter, but she expects to do so soon. She reports, "I feel much better than I did previous to the dust-proofing of my bedding." No examination of her blood pressure has been made since May 4, 1947.

Case 3.—The third case, A. B., also a patient of Dr. Dickson, is a man of fifty-seven whose blood pressure had been constantly 180/100 or higher and had stood at 220/116 on his first visit to my office. He had had several "attacks of fainting" in which he fell. His eyes were regularly "blood-shot" on rising in the morning. He had had urticaria, indigestion, neuralgia and occasional abnormal tiredness, constipation, and headaches. He feels better in the summertime.

From the beginning of the pulse-dietary course, the pulse generally ranged from 72 to 84, with an occasional 86 or 88 having no relation to the diet. On the third, fourth and fifth days the retiring and before-rising counts were:

March	*24*	*25*	*26*
Before rising	82	80	80
Retiring	76	72	78

This record indicated a moderate acceleration of the pulse due to an inhalant allergen originating in the bedding, and dust-proof covers were ordered and were put on the bed on the eighth day. The before-rising pulse counts on the subsequent six days were, 72, 72, 74, 72, 70, 68. These were always lower than the preceding retiring counts, 80, 78, 80, 78, 78, 82.

The blood pressure taken on the day following the covering of the bedding was 160/110. One month later it was 166/106, and an experimental air filter was installed. At that time two uncovered mattresses were discovered in the living room and were ordered into the attic. Two weeks later the pressure stood at 140/92. Since that time there have been intermittent exposures to paint fumes, rotenone, and commercial fertilizers, sometimes with accompanying mild tachycardia (up to 88) and increased blood pressure. His blood pressure readings in July, 1947, were:

1—148/72†	6—159/92	10—162/86	19—142/82	28—150/92
4—168/82	8—158/92	15—166/90	21—162/98	29—168/86

†At beach all day.

On July 26, the pressure at 9:00 a.m. was 164/94. After he had worked in the garden all day with rotenone and commercial fertilizer, the pressure was taken by two observers with two instruments with the following results:

Observer A with instrument B 178/102
Observer B with instrument B 180/104
Ten minutes later:
Observer B with instrument A 190/98
Observer B with instrument B 190/98

The patient is pleased with his much improved general well-being and freedom from the minor symptoms mentioned above. While it seems possible under ideal environmental conditions to reduce the hypertension in this case much further,

any such effort might be economically prohibitive and would almost certainly not be undertaken by the patient in his present satisfactory state of health. Although in all of the foregoing case reports the environmental allergic excitant has been spoken of as "house dust," the question of its exact identity has not been raised. The omission was deliberate; all efforts to solve this mystery have failed. For the practical purpose of avoidance, however, it is sufficient to know that that objective can be attained by dust-proofing plus air filtration.

Similarly, in the following case the environmental excitant was not exactly identified, but its source could be determined and avoided. The chief complaint of this patient was a dermatitis. In view of the notorious pitfalls of dermatological diagnosis and my own inconsiderable experience in it, I shall content myself with a description of the lesions in the case.

Case 4.—Patient L. M. P., aged sixty-one, was referred on May 9, 1946, by Dr. H. E. Bejack, New York, N. Y., with a history of "allergic dermatitis" unimproved by various treatments over a period of about two months.

The patient presented a scaly, itching eruption of forearms, thighs (inner surfaces) and back of neck (skin thickened) with angioneurotic swelling of cheeks and eyelids. The pulse ranged at first from 54 to 97. The pulse-accelerating allergens were found to be cereals, orange (itch), honey (itch), fowl, lamb, a popular shaving cream (pulse 108), soap (exposure to soap powder caused itching and prolonged acceleration of the pulse). Almay shaving cream caused no reaction.

Within three weeks after beginning the pulse-dietary course, the eruption was healing everywhere and the angioneurotic edema had disappeared. The normal pulse range averages 50 to 63 but slight contact with some inhalant allergens probably continues, raising the rate occasionally to 66 or 68. All lesions finally disappeared, leaving only a negligible perineal pruritus. The pretreatment blood pressure taken by Dr. Bejack at about weekly intervals was 130/70, 115/85, 115/85 and 120/85. In my office May 10, it was 140/85. The pressure after treatment has been 122/66, 110/64, 110/70 (Dr. B.), and 120/70. No skin tests were done. The patient has remained entirely well (latest blood pressure 112/66) throughout the succeeding seven months. There was no local or other medication.

It is worthy of note that whereas soap powder as an air-borne inhalant allergen caused both tachycardia and exacerbation of the dermatitis, the same soap in bar form could be used by the patient without either of those consequences.

CONCLUSIONS

1. Allergic (essential) hypertension has been shown to be caused, not infrequently, by air-borne specific excitants, sometimes in subjects who are not allergic to any foods in their diet.

2. Extensive dust-proofing of bedding and upholstered furniture did not provide adequate protection against house dust in the three cases cited. A portable air filter is described with which the desired result was obtained in the two cases for which it was used.

3. One instance is cited in which an air-borne allergen (soap powder) could be reasonably suspected as specific excitant of "allergic dermatitis" (neurodermite?).

NOTE: This study is continued and concluded in the succeeding paper on Dust-Seal.

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DUST-SEAL
Its Use in the Avoidance of "House Dust" by Dust-Sensitive Persons

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IN a previous publication[3] a few instances of nonreaginic sensitivity to that mysterious inhalant allergen known to allergists as "house dust" were described, in which the dust-proofing of bedding and upholstered furniture alone markedly lessened the patients' symptoms. However, the circumstances in one of these (A.F.C.) indicated a continuing, if lessened, exposure to dust, the effects of which were serious enough to suggest the installation in the house of a fiber-glas air filter for the removal of dust originating elsewhere than in the bedding and upholstery.

The clinical result of this measure was highly gratifying; the average blood pressure was reduced from 149/81.7 to 142.5/76, and the patient was free from chest pain, conjunctivitis, and gastrointestinal disturbance—this in spite of his living in the house, whereas he had previously been obliged to live in the partly closed-off sunporch.

There remained the inconvenience of his having to shun the house during the several hours following the periodic vacuuming, while the filter was running for the removal of the scattered dust particles which had escaped the cleaner. On some occasions it was necessary for the patient to be in the house during this operation or too soon afterward. These happenings were regularly followed by immediate chest discomfort and by diarrhea on the next morning, and these frequently recurring sequences suggested that allergenic "dust" may originate also in the floor coverings.

It was at this juncture in November 1947, that I had a conversation with Mr. Leonard S. Green,* concerning the remarkable properties of a product of this organization in the reduction of the bacterial content of the air in enclosed rooms and the consequent lessening of infections in the personnel occupying them.

Mr. Green has kindly contributed the following summary of information concerning this matter.

"Effective means for controlling the bacterial-dust phase of air contamination, in an endeavor to minimize the acute respiratory infections among all personnel in test areas, were first studied by Van den Ende and Andrewes[6,7] in England and later by the U. S. Army and Navy. The best procedure was determined to be the use of absorptive oils as a means of choking off secondary reservoirs. This might take the form of depositing an oil imperceptibly on floors or in fabrics, or both, depending upon

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Dust-Seal is the trade name of a product of L. S. Green Associates.

*President of L. S. Green Associates, Air Sanitation Products, 160 West 59th Street, New York 19, N. Y.

the environment. A hospital, for instance, on account of the volume of textiles used, can take full advantage of the new practice.

"No bactericidal action is claimed or contemplated in the application of modern oiling methods. The absorption and retention obtained, however, is quite high. Dr. Henry Wise, former member of the Commission on Air-Borne Infections, reports that the reduction in the number of bacteria which could be liberated from a treated blanket amounts to 75 to 95 per cent as compared to an untreated blanket exposed for the same period of time under similar surroundings. These foreign particles (bacteria, dust) can be easily removed with soap and water in a normal washing operation; but wool has the peculiar property of retaining a large portion of the recommended oils after *water washing,* so that very little re-introduction of the oil is necessary. However, the oil would be completely removed with dry cleaning. Cottons behave differently; a larger portion of the oil is removed by water washing and, therefore, a larger portion must be put back. The above-mentioned determination of retentivity was made with the suction of a vacuum cleaner and by dropping steel balls on contaminated blankets over exposed Petri dishes.

"Working in barracks and hospital wards under conditions of adequate control, the investigators report reductions in bacterial counts (taking them both by plates and Folin bubbler samplers) of 50 to 90 per cent. This improvement in air purity was accompanied by fewer hospital admissions at Camp Carson, Colorado,[5] than in the group used for control (5,750 men in both areas). In this project not only floors, the oiling of which reduced bacterial dispersion by 70 per cent during hours of maximal activity, but also blankets, mattress covers, sheets and pillow cases were treated. The impregnation of the fabrics alone added another 10% to the bacterial reduction.

"The investigators in England, working in barracks with individuals subject to outside exposures, established an infection rate of 7 per 1,000 in test groups of 1,300 to 1,700 men, as against 38 per 1,000 in the control group, or a difference of about 80 per cent.[1] As yet no similar data in degree of performance have been developed or published in this country.

"Impressed by the apparent efficacy of a microbic glue, to be used as a part of good housekeeping practice, this firm was organized to determine the type of oiling compound needed for civilian environments. The oils used for coating barrack floors were found to be impracticable, since both walk-quality and appearance had to be considered along with labor costs in application.

"The first formula used was an oil mixture, which is easily emulsifiable in water. When the milk-white, odorless emulsion is sprayed or sprinkled to thorough soaking upon rugs or carpets or upholstered furniture, it quickly becomes quite invisible. Since the oil is nonvolatile, the fabric is not made more than usually inflammable.

"The emulsion is quickly prepared, as follows: A suitable pot is filled

about two-thirds full (one quart) with warm water from the faucet; place four or five heaping tablespoonfuls of the commercially distributed cream on the surface of the water and emulsify (two to three minutes) with an egg-beater. Make up with water to one gallon and distribute with fine-holed garden watering pot. For effective treatment, rugs and carpets must be thoroughly soaked. Such treatment has not caused noticeable injury to even fine Chinese and Turkish rugs."†

CASE REPORTS

Case 1.—The first person with nonreaginic dust sensitivity in whom the protective action of Dust-Seal could be observed was patient A.F.C. This case was most favorable for the purpose of the particular experiment, because of the easily observable, one may even say measurable, consequences of his exposure to dust, which have been described in a previous report.[3]

Dust-Seal was first applied by the patient to the rugs with a "flit-gun" on two successive days. This amounted to a mere surface dampening of the rugs that produced no encouraging change in the average blood pressure. Two months later, on January 15, 1948, all the rugs were thoroughly soaked with the emulsion.

In the period from January 19 through March 25, the recorded blood pressures were:

Systolic	*Diastolic*	*Systolic*	*Diastolic*	*Systolic*	*Diastolic*
122	72	138	74	130	70
132	78	146	68	130	78
130	72	146	70	130	76
136	78	130	78	146	76
136	72	146	80	142	70
126	72	132	68	124	70
138	80				

The average of these readings is 134.5/74.

This reduction of the blood pressure becomes the more significant of a diminished exposure to dust, as a result of the immobilizing effect of Dust-Seal, when the fact is considered that since the Dust-Sealing the use of the air-filter has been entirely discontinued. Moreover, the patient remains in the house while the vacuum cleaner is in operation without experiencing the slightest symptom of his dust-sensitivity.

Case 2.—Patient A.B. has been described also in the previous report.[3] This man's systolic pressure, which had been constantly 180 or higher, had dropped to an average of 158.3 after the dust-proofing of his bedding and upholstered furniture and the installation of a fiber-glas air filter. He was not food-allergic.

On March 5, 1948, the heavy carpeting of the patient's bungalow was thoroughly soaked with the Dust-Seal emulsion under the personal direction of Mr. Green. The average of the previous twenty readings of the patient's systolic pressure was 160 (range 148 to 170). From March 16 to March 25, the daily systolic pressure readings average 143 (range 140 to 148, with one reading of 158).

Case 3.—V.H.S. suffered with chronic rhinitis, canker sores, headaches, nervousness and abnormal tiredness. Skin tests showed her to be dust-sensitive; her husband and son had also been found skin-test-positive to dust. However, she has a nonreaginic sensitivity to dust, which is seen in a pulse rate of 102 observed "after making beds." Her normal pulse ranges from 64 to 80. No nonreaginic food sensitivities have been discovered. The patient reported some improvement of her symptoms after replacing her down pillows with air-filled ones.

In March, 1948, she applied dust-proof covers to mattresses, pillows and cushions and wore a dampened mask while dusting and making beds. "This seemed to

†For more details concerning the treatment of various fabrics with Dust-Seal, see the manufacturer's special literature.

TABLE I. PULSE RECORD OF V. H. S. IN MARCH AFTER APPLICATION OF DUST-PROOF COVERS, AND IN MAY AFTER APPLICATION OF DUST-SEAL

	March				*May*			
	27	28	29	30	19	22	25	27
Before rising	60	60	62	60	—	—	—	—
Breakfast			90					
	76	78	80	78	80	82	76	—
	80	90	90	82	76	76	80	—
	90	80	90	84	76	72	74	66
	80	78	—	80				
Cleaning,					76	76	70	80
making beds	90	98	100	90	No mask used			70
	—	92	84	—				
Lunch	76	76	76	—	—	—	—	—
	84	80	82	—	82	78	—	78
	80	84	78	—	80	74	—	80
	—	74	—	—	76	74	—	74
Mid P.M.	—	80	—	—	78	—	74	72
	—	74	—	—				
	—	74	—	—	—	—	—	—
Dinner	—	74	78	76				
	—	82	80	74	72	74	80	74
	—	80	80	74	74	72	78	78
	—	74	76	74	72	72	76	74

— indicates no record made.

help a great deal," symptomatically, though the pulse remained generally high and erratic.

Dust-Seal was liberally applied to floor covers about April 20, and a few weeks later "blankets and slip covers were washed and rinsed in the emulsion."

The pulse record of V.H.S. in Table I shows the effect of the Dust-Seal on the pulse rate. It is noteworthy that the high rates in March always occurred in the morning, the period of greatest exposure to dust.**

In June the patient wrote, "I am delighted about the improvement of my husband and son—they are both allergic to house dust by skin test, having a hay-fever condition most of the winter. Three times, I have noticed an improvement. First, when I eliminated down pillows and quilts. Second, when I covered the mattresses. Third, when I used the Dust-Seal." As for her own chronic rhinitis, she writes it is "better than it has been for a year."

Case 4.—M. M., aged thirty-nine, had bronchial asthma with chronic rhinitis. She had consulted an allergist who found her skin-test-positive to feathers and cheese; she had received a series of injections. Consulting me on August 31, 1946, she reported that she had suffered a severe attack of asthma over several days at the time of her August period (a coincidence that recurred in the next two months). The pulse in these attacks was high (in the nineties from a normal low of about 60). The October attack culminated in an alarming status, making it imperative to all concerned to decide upon the most probable cause of the "attacks" and take appropriate action.

The usual dust and feather precautions had been instituted; there were no food allergens in the diet, and the cutaneous tests to ragweed pollen, as well as to grasses and oak, were quite negative. Inhalation of vaporized ragweed pollen extract caused no asthmatic symptom. The most likely cause of the attacks seemed to be an "internal allergen" appearing at the periods. The patient has two children, and she and her husband agreed to artificial menopause with a series of x-ray treatments, which were administered.

Two further periods were experienced, both accompanied with milder asthmatic attacks and pulse rates up to about 104. Thereafter there were no periods nor frank asthmatic attacks.

However, the chronic rhinitis with mild wheezing continued, and the cause of

**It is also noteworthy in this connection that in the investigation at Camp Carson mentioned in Mr. Green's summary, "the bacterial content of the air during the bedmaking was 1200 per cent greater than during a quiet period in the same ward with the same occupancy."

these symptoms was believed to be house dust, the scratch-test for which caused a 3/8-inch wheal with a two-inch flare.

Installation of a fiber-glas air filter caused no noticeable relief of these symptoms, but they ceased shortly after the thorough Dust-Sealing of the floor coverings on February 15, 1948. Previous to that time the patient had had some symptomatic relief with the use of an "iodide prescription" obtained from another physician. She has not used this since. Five months have passed with no recurrence of any of her symptoms.

Case 5.—G. M., the four-year-old son of the foregoing patient, had had occasional asthmatic attacks previous to the institution of the dust precautions (cutaneous tests have not been done). There was no asthma thereafter, but whenever he played with his teddybear, pushing his nose deep into the fur, he had continuing spells of sneezing. Recently his parents dipped the teddybear into a pot of Dust-Seal emulsion and dried it. Thereafter the boy played with the thing as intimately as before but without ever sneezing.

Case 6.—Mrs. McC., aged twenty-four, had the following symptoms: abnormal tiredness, headaches, indigestion, asthma, chronic rhinitis, dizziness, urticaria, angioneurotic edema. Her most alarming symptom was spells of partial blindness, the nature of which was not determined because she has never been competently examined in an attack. The pulse survey failed, and resort was had to conservative sympathectomy after a successful survey following two ganglion blocks by Dr. E. A. Rovenstine. Since then the patient has experienced only one attack of blindness, which followed shortly after the eating of egg, to which food she is still sensitive.

Her nonreaginic sensitivity to dust was indicated by the observation that her pulse was regularly higher before rising in the morning than it was just before retiring. Bed-mattresses and pillows were dust-proof covered, and there were no heavy rugs on her apartment floors. Nevertheless, there was still some dizziness, tiredness, very slight "headachy" feeling and a melancholic depression which was more marked at the periods. Finally the one large piece of furniture, an antique divan, came under suspicion as a possible source of allergenic dust. Into this divan one and a half gallons of Dust-Seal emulsion were poured, and the piece was dried out under a warm sun.

Immediately after this operation and in the succeeding three months, the patient was quite free from the listed symptoms, experiencing only some irritability at the periods.

The evidence for the effectiveness of Dust-Seal in this case is of questionable value, because it is lacking in real objectivity, resting to only a limited degree upon the husband's positive assertion and involving the more interesting question, whether the several "psychoneurotic" symptoms can actually be caused by an inhaled allergen.

DISCUSSION

The experiences here described mark the product Dust-Seal as an efficient, economical, harmless and easily applied immobilizer of allergenic dust in fabrics in which that allergen is presumably generated.

In the cited cases the Dust-Sealing was applied to sources of the allergen which are not closed off by the familiar dust-proofing. However, there seems to be no reason why mattress fillers and also upholstery stuffing cannot be Dust-Sealed, without appreciably increased cost.

(Continued on Page 517)

REACTIONS TO HISTAMINE IONTOPHORESIS IN THE THERAPY OF MULTIPLE SCLEROSIS

Preliminary Report

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THE search in recent years for a theory which would explain the origin of multiple sclerosis has led to a proposal that the disease may be connected with an allergic reaction to the products of the patient's own central nervous system, or to allergic phenomena connected with bacterial infection. Thus, at the fourth annual session of the American College of Allergists there were presented papers[11,13,14,15,17] dealing with the theory, origin, and the therapy of multiple sclerosis with these specific aspects.

The work of Horton and co-workers[7,12,16] stimulated the writer to explore the possibility of developing a therapeutic technique of administering histamine by iontophoresis rather than by the intravenous route, for several reasons: (1) the veins need not be punctured; (2) the apparatus is inexpensive; (3) hospitalization is not required; (4) sterile equipment need not be employed; (5) the dose of the drug administered can be readily controlled by concentration, current density, time and electrode area; (6) histamine administered iontophoretically forms depots in the skin;[1,4,5,6] (7) it is adapted for home use, and the technique can be easily carried out either by the patient alone or with the help of the family.

The therapeutic principles of Brickner and Franklin[8,9,10] were used as a guide in therapy.

METHOD

In general, the previous technique described by the writer[2,3] for the iontophoresis of epinephrine in asthma was employed, with certain modifications required for histamine. Only one lead of the equipment was used, although it is possible to treat three separate areas of the skin, either in succession or simultaneously. Canton flannel, 3 inches wide and 12 inches long, was folded twice over lengthwise, so that the final area was approximately 12 square inches (3 inches by 4 inches). This was applied to the anterior aspect of the forearm with the required concentration (up to 1 per cent) of histamine acid phosphate* solution, and contact was made with an electrode of aluminum foil which was held by a rubber pad and strap against a flat copper positive plate. Current up to 8 milliamperes with this area has been employed, although not more than 5 milliamperes have been recommended for home therapy. The current

The author is indebted to Mrs. Erna Teige for assistance in the research program.
*Ergamine, kindly supplied by Burroughs-Wellcome.

density, therefore, has generally not exceeded ⅔ of a milliampere per square inch. This current density may be exceeded, but it is believed that no change should be made until further investigations have been made on the patient's general reactions and blood pressure.

The blood pressure, pulse rate, oscillometric index and temperature were followed, as well as the subjective response of the patients. The patient was told to expect a flush and possibly throbbing of the blood vessels in the head. This relieved most of the anxiety connected with the first experience of the flush. In general, the length of each treatment was fifteen minutes, with the concentration of the solution increased in three steps from 0.25 to 1 per cent, with the current increased from 2 to 8 milliamperes, depending upon the reaction of the patient. Oscillometric readings were obtained in the upper part of the arm and forearm. Certain patients complained of abdominal discomfort, which was probably due to the liberation of gastric juice. An antacid mixture of glycine, three parts, calcium carbonate, seven parts, was routinely administered in the form of tablets†, two before and two after therapy. Further details of the investigative and therapeutic plan will be presented in the brief descriptions of cases studied during the past year.

Eleven cases have been treated during the past year, details of which will appear in a subsequent publication. In order to enable others to follow the procedure, the following cases (Nos. 4 and 10 in the series) are presented.

CASE REPORTS

Case 1.—J. S. was a thirty-six-year-old married woman with two children. She had had multiple sclerosis for approximately four years. Two years before she was seen by the author, she improved slightly following a course of intravenous histamine. She had much difficulty in walking when she was first seen by the writer and was unable to use the subway or go shopping. Treatment was begun on July 12, 1948, with 0.25 per cent histamine solution, the current being 2 milliamperes for fourteen minutes. With this dosage the primary flush appeared at about seven minutes. The relationship of the blood pressure to the dose of histamine and the onset of the flush is given in Table I. Note that with increased dosage the flush usually begins earlier and the drop in blood pressure is, in general, more noticeable. The oscillometric index was essentially unchanged. The plan of initiating therapy, prior to permitting home therapy, is well brought out in Table I, which should be consulted for details. It is of importance that this patient took approximately 100 milligrams of niacin daily during the time of, and simultaneously with, her histamine therapy, and that she was able to take two treatments per day without immediate untoward effects. Shortly after beginning therapy the patient seemed much better and was not as much fatigued on walking about. She was able to use the subway and to go shopping alone. She stated, "My legs don't jerk as much from the joints." Her vision was much improved. At present she has been placed on home therapy.

It might be argued that the improvement in this patient may be due to factors other than those connected with the administration of histamine. For example, niacin,

†Titralac, kindly supplied by Schenley Laboratories.

TABLE I. BLOOD PRESSURE, DOSAGE PLAN AND FLUSHES: CASE 1
The Patient Received Equipment for Home Therapy

Date	*Before* mm. Hg	*After* mm. Hg	*Dose* Histamine as the Acid Phosphate	*Primary Flush* After Therapy Began Approximateyl (Minutes)
7/12	118/84	115/84	0.25% 3 ma. 15 min.	7
7/13	120/84	115/70	0.5% 2 ma. 15 min.	7
7/14	118/88	118/72	0.5% 3 ma. 15 min.	6
7/15	115/88	102/70	0.5% 3 ma. 15 min.	7
7/16	115/84	112/60	10 pellets (2.75 mg.) 3.5 ma. 20 min.	10
7/17	118/82	115/68	0.5% 4 ma. 15 min.	10
7/19 a.m.	115/78	112/70	1% 3.5 ma. 15 min.	5
7/19 p.m.	115/78	115/60	1% 4.5 ma. 15 min.	5
7/20 a.m.	112/70	100/56	1% 4.5 ma. 15 min.	6
7/20 p.m.	110/78	110/60	1% 3.5 ma. 15 min.	6

was taken simultaneously. It was quite possible that this striking improvement was due to a synergism between histamine and niacin. Dr. R. M. Brickner, who was kind enough to refer this patient for therapy, informed the writer that, in his opinion, the improvement was not a spontaneous remission but was probably due to the pharmacologic action of the histamine. Further data, of course, must be obtained, and the future history of the patient under this type of therapy must determine whether or not the therapeutic technique is responsible for the clinical results.

Case 2.—E. W. was a twenty-five-year-old married woman who had had multiple sclerosis for five years. Her first symptom occurred when she collapsed in the street, three months after her marriage, and could not move her legs. She was able to walk afterwards, but poorly. The diagnosis of multiple sclerosis was made at that time. She had had two previous series of treatments with histamine intravenously, without any improvement. The iontophoretic treatment was begun with 1 per cent histamine acid phosphate solution administered for ten minutes, with a current of 3½ milliamperes. The blood pressure was 96/60 before her first treatment and dropped to 84/48 at end of therapy. She felt slight dizziness after therapy but was able to walk readily. She stated at the time that she felt that "hope was gone." The next day her dosage was increased to 4½ milliamperes for fifteen minutes. She then mentioned that she had been frightened by an intern whom she had overheard saying that he would rather have a brain tumor than multiple sclerosis. Since that time she had been exceedingly depressed. Four hours later on the same day the patient took a second treatment. The blood pressure at the beginning of this second treatment was 100/68 and at the end was 84/54. During this treatment there appeared sudden movements of the joints of the arms and legs. The patient received successive treatments on the two following days and then a fifth treatment four days later. At this time the patient felt that there was no improvement. She stated that she had had

histamine before with no improvement and there was no improvement this time either. She felt, however, that in spite of the rather severe reactions that she had, she was not any worse. During the treatment on July 26, 1948, the left leg jerked during the flush and there was twitching of the left side of the face. The sixth treatment was given on July 28. The patient remarked that she was frightened about her multiple sclerosis. On July 29 the patient said that she had had a secondary flush following her treatment of the previous day, and mentioned that she believed that the histamine had damaged her heart. On coming to the office that morning she had sensations of a tight feeling in the throat and of choking.

This case is representative of an instance in which the patient states that no improvement occurs during therapy, and ostensibly is in direct contrast to the previous case described. However, this patient walked seventeen blocks by herself following the ninth treatment. It is evident that she has a severe anxiety neurosis as well as multiple sclerosis. In addition, she has been subjected to many traumatic situations incidental to her disease, all of which makes it difficult for either the doctor or herself to evaluate the results of therapy. She is planning to continue the therapy at home, after a suitable number of treatments have been administered under medical supervision.

DISCUSSION

There are nine other cases under therapy (as this report is written), all of whom show, to a certain extent, better muscular co-ordination, better ocular co-ordination, or both.

The therapy of multiple sclerosis by histamine is not a desensitization to an allergic reaction. Indeed, the use of histamine iontophoretically in ordinary allergic reactions, such as those occurring in the bronchial tree, is contraindicated here, because in all likelihood asthmatic attacks would be produced. It is recognized that small doses of histamine have been used to desensitize the patient to various allergic syndromes. However, the pharmacologic effect of histamine, as administered by Horton and his co-workers and as administered here, is dependent upon the maintenance of vasodilatation by a pharmacologic reaction.

Our present purpose is to give the patient at least ten office visits before a galvanic machine is recommended for the use of the patient at home. The following memorandum is given to the patient:

Directions to Patients for the Self-Administration of Histamine in the Therapy of Multiple Sclerosis

1. Attach the electrodes to the iontophoresis machine, making certain that the red plug matches the red socket. This is the positive pole. The negative pole is the inert reference electrode and can be placed anywhere on the body or as demonstrated to you in the doctor's office. The positive pole may be placed in the anterior aspect of the forearm. If you decide to use another location of your body, please come to the office so that your reaction to that site may be tested, since absorption varies in different parts of the body. The rate of the absorption from the site must be predictable. For example, if the histamine is administered in the thigh the absorption of the histamine will be accelerated.

2. Obtain a piece of canton flannel, 12 inches long and 3 inches wide, and fold over as directed. Have a sheet of aluminum foil ready for the positive pole of the galvanic machine.

3. Dissolve 1 gram of histamine acid phosphate (Ergamine Phosphate—Burroughs-Wellcome) in 100 c.c. of distilled water. If distilled water is not available, tap water may be used temporarily. Measure 10 c.c., or approximately 2½ teaspoonfuls, of this solution, using a plastic measuring spoon, and spread uniformly on the dry Canton flannel. Keep the remaining solution in the refrigerator.

4. Place the canton flannel, wet with the solution, on the anterior aspects of the forearm; place the negative reference electrode on the designated place, making certain that there are no cuts or pimples under the electrode area. If metal touches the skin, or if there are bruises or pimples, there will be a concentration of electricity in that area and an intense burn will be felt. All jewelry should, therefore, be removed. Otherwise, the reaction, as you know, is simply itching with slight irritation.

5. After the electrodes are firmly in place, make certain that the rheostat is down to zero and turn the current on. Slowly increase the current. If burning occurs, make certain that the electrodes are uniformly in contact with the skin and that there are no breaks in the skin. Increase the current slowly to 5 milliamperes. This should not be exceeded before discussion with the doctor.

6. Maintain this current for fifteen minutes, or as otherwise directed.

7. If fainting occurs, an injection of ½ c.c. of epinephrine 1:1000 will instantly relieve the symptoms due to the histamine.

8. Keep the following record of each treatment:

Name .....
Time, beginning of treatment: .....
Time, completion of treatment: .....
Total time: .....
Flush appeared after .....minutes.
Current of.....milliamperes.
General reaction after therapy: (Include occurrence of secondary flushes).

It is believed that prolonged iontophoretic therapy with histamine combined with vasodilatation by mouth (e.g., Niacin) provides a greatly simplified form of therapy with therapeutic possibilities equivalent to intravenous therapy. It may also prove effective in other degenerative diseases of the central nervous system, as well as in obliterative vascular disease.

SUMMARY

The successful therapy of multiple sclerosis by the intravenous administration of histamine has led to the development of an iontophoretic technique of administering histamine in this disease. The use of the electric field to introduce histamine into the human skin has certain advantages: (1) the veins need not be punctured for prolonged periods of time; (2) the apparatus is inexpensive; (3) hospitalization is not required; (4) sterile equipment need not be employed; (5) the dose of the drug administered can be readily controlled by varying concentration, current density, time and electrode area; (6) histamine administered iontophoretically forms depots in the skin; (7) it is adapted for home use for the technique can be easily carried out either by the patient without help or with the help of the family.

Previous investigations have shown that histamine introduced by iontophoresis into the skin forms depots in the pores of the skin. On the basis of the therapy of eleven patients with multiple sclerosis, one of whom had as many as fifty-five treatments on the anterior aspects of the forearm, 1 per cent histamine acid phosphate solution may be readily administered by electrophoresis with a current density of ½ milliampere per square inch for fifteen minutes at a time. The following phenomena occur:

1. A typical histamine primary flush occurs within five to ten minutes after the drug is electrically administered.
2. Small doses decrease the diastolic pressure, while the larger optimal doses decrease both the systolic and the diastolic pressures.
3. In spite of the drop in blood pressure, the patients remain ambulatory.
4. The reaction of the patient is better to the higher doses and consists, in general, of increased muscular co-ordination and strength and improved use of the eyes, as far as vision is concerned.
5. An interesting phenomenon, apparently hitherto not observed, is the occurrence of secondary flushes. With the high doses employed, half of the patients reported frequent occurrence of a flush five to twenty-four hours after histamine iontophoresis. These secondary flushes provide further evidence that the electrical technique produces depots of histamine in the pores of the skin.

The iontophoretic technique is equivalent to intravenous drip therapy, with more flexibility. According to Brickner and Franklin[9] and Franklin and Brickner,[10] the basic notion in the therapy of multiple sclerosis "calls for continued vasodilatation of the vessels of the nervous system, as well as for the prevention of spasm. Both these measures should be enforced for twenty-four hours a day. A drug-free interval of even a few minutes would suffice for an attack."

It is believed that the technique now being developed may lead to the ultimate fulfillment of the criteria of therapy suggested by Brickner and Franklin.

The writer is indebted to Dr. M. B. Bender and Dr. Richard M. Brickner, who were kind enough to refer patients with multiple sclerosis for therapy.

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DUST-SEAL

(Continued from Page 510)

There are no reliable statistics from which the incidence of nonreaginic dust sensitivity can be estimated. If it equals that of reaginic sensitivity in the atopic group (about 25 per cent), physicians may reasonably urge the use of only Dust-Sealed bedding and upholstery in all dwellings and hospitals. The simple Dust-Sealing of floor coverings is no problem.

SUMMARY

A new product, Dust-Seal, has been found to immobilize allergenic house dust in floor coverings and other fabrics, as indicated by lowering of blood pressure, slowing of pulse rate and disappearance of allergic symptoms, in dust-sensitive persons.

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SENSITIVITY TO MERCURIAL DIURETICS

Report of a Case of Urticaria Due to Mercupurin

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IT is probably safe to say that mercury has been employed medicinally in a greater variety of compounds and by way of more routes of administration than nearly any other element. Mercury in various forms may be applied directly to the skin as a liquid or ointment, or by inunction or tattooing; it is also administered by mouth, by intramuscular and intravenous injection, and by rectal suppository. Interesting cases of sensitivity to mercury by injection were reported as early as 1895 by Jadassohn,[31] and constitute some of the early clinical material on which the concept of patch testing was based. Mercurial compounds are notorious epidermal sensitizers, and in several recent series of cases led all other cutaneous drugs as a cause of therapeutic dermatitis (Gaul,[25] Lane,[33] Underwood et al[56]). Moreover, sensitivity to mercury may be of extreme intensity. Not infrequently, cutaneous hypersensitiveness may be so great that patch tests with a 1:1,000,000 dilution of either organic or inorganic mercurial compounds may produce bullous reactions and even focal flares of distant dermatitis in some cases (Gaul[25]). Another example of the incredibly small quantities capable of producing severe manifestations is a case cited by Sulzberger.[48] One day after merely spending an hour in a room in which a small quantity of Mercurochrome had been spilled several hours earlier, this patient had generalized dermatitis, lymphadenopathy, prostration and high fever. Even pure metallic mercury has been responsible for cutaneous eruptions (Traub and Holmes,[52] Billo,[7] Bass[4]). Evidence of mercurial poisoning may accompany the contact dermatitis, as in a case observed by Samitz[45] due to ammoniated mercury ointment. Most recent reports of sensitization implicate cutaneous antiseptics, such as Mercurochrome (Pasher and Silverberg[43]), Mercurophen (Gross[27]), Merthiolate (Ellis and Robinson,[19] Hollander,[29] Lipson[35]), Metaphen (Belote and Marshall[5]), and phenyl mercuric nitrate (Hydrophen) (Wilson[60]). However, the mercury content of cosmetics may be responsible (Cifrián,[15] Schwartz and Peck[46]) and, as already mentioned, so may the mercury in dermatologic preparations as well as industrial contactants. Epidermal contact need not invariably produce dermatitis. In a woman observed by the author,[57] urticarial wheals occurred on the patient's hands, forearms and groin each time she applied ammoniated mercury ointment to her child's impetigo. A patch test with this ointment produced not a vesicular dermatitic response, but a typical urticarial wheal within twelve hours. Both local and distant cutaneous manifestations and even systemic allergic reactions have been noted to follow

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inunction of mercurial ointment (Billo[7]) and tattooing with cinnabar (Novy,[40] Sulzberger et al,[49] Swinny[51]). The mercury contained in mercury amalgam dental fillings has been found to cause urticaria (Bass,[4] Markow[36]) and dermatitis, sometimes with stomatitis, from contact with the mercury during the dental manipulation (Blumenthal and Jaffé,[9] Traub and Holmes[52]). Mercurial rectal suppositories are also capable of eliciting allergic reactions (Blackford,[8] Kline and Seymour,[32] Fox et al[24]).

In view of the length of this incomplete list of proved sensitivity to mercury, it is surprising that allergic reactions to parenterally administered mercurial diuretics are, in the opinion of all observers, rare. Thousands of injections have been given by some investigators[32,16,18] without noteworthy untoward effects. Some individual patients have been known to tolerate hundreds of doses over periods of several years without incident. The allergic manifestations, when they do occur, are quite varied, as will be noted below, and may be mild, alarming or even fatal.

POSSIBLE MECHANISMS OF REACTIONS

However, it must be emphasized that drugs as physiologically potent as mercurial diuretics are capable of producing untoward reactions by a number of mechanisms. For clarity of analysis, it is profitable to consider these briefly. DeGraff and Nadler,[16] in a thorough review of the toxic manifestations of mercurial diuretics, classify them as fundamentally resulting from the associated diuresis or directly due to the drug. Such symptoms as disturbances of salt balance (particularly chloride depletion), precipitation of gout, and overdigitalization are considered the result of diuresis, while gastrointestinal complications (e.g., stomatitis, salivation, and hemorrhagic colitis), renal complications, anuria, chills, fever, and shock are traced to the drugs themselves. However, these authors point out that, in common with other potent drugs, individual susceptibility or idiosyncrasy occurs with mercurial diuretics, and that all commercially available drugs of this group have been implicated in isolated instances of alarming symptoms and even death, in some cases apparently due to susceptibility. Evans and Perry[22] classify the untoward effects under six headings: (1) local ulceration, due to seepage of the drug into perivenous tissues; (2) muscle pains, somnolence, delirium, occasionally coma, and sometimes tetany or epilepsy, due to chloride depletion resulting from the diuresis; (3) in digitalized patients, digitalis toxicity, due to mobilization of digitalis from edema fluid; (4) various reactions such as fever, rashes, tremor, tinglings in the arm, stomatitis, nausea, vomiting, diarrhea, colitis, sensations of thoracic constriction, swelling of the lips, and anuria, some of which are undoubtedly on the basis of a direct toxic effect; (5) precipitation of an attack of gout; and (6) death. They believe the cause of death to be obscure, but state that it may be an acquired sensitivity. However, none of their cases died after his

first injection of a mercurial diuretic, suggesting acquired sensitivity as a probable cause of the phenomenon. According to Marshall[37] mercurial diuretics may cause tetany, manifested by muscle "cramps" and carpopedal spasm, as a result of low blood calcium levels. Such electrolyte imbalance may occur prior to diuresis, although obviously it will be enhanced by excessive urine flow, and may explain one of the modes of exitus. The nature of the required therapy is apparent.

It should be noted that these drugs are capable of producing death in animals by reason of the primary poisoning effect of mercury on the heart, producing ventricular fibrillation. That this mechanism applies to some human fatalities was clearly shown by Volini et al.[58] On the basis of animal experiments, Chapman and Shaffer[13] found Mercuhydrin to be less toxic than Mercuphylline or Mersalyl and theophylline, and that its toxicity was still further reduced by ascorbic acid given simultaneously. They suggest that since nonfatal hypersensitivity reactions, such as tachycardia or premature ventricular systoles occurring after intravenous administration, may be premonitory signs of a fatal reaction, Mercuhydrin combined with ascorbic acid is the diuretic preferred in such cases. This suggestion requires confirmation. It is also possible that death may occur by respiratory failure secondary to the impaired cardiac action which is presumed to lead to anoxia through lowering of the blood pressure. It has been emphasized[18] that in the majority of deaths in man following the administration of mercurial diuretics, the blame could be placed on the moribund condition of the patient, on digitalis poisoning, on depletion of chloride, or an oliguria or anuria leading to faulty elimination of the diuretic itself, or on the presence of kidney impairment sufficient to prevent adequate excretion of the drug or to predispose to such damage by the mercurial. Certainly, sensitivity to mercurial compounds as a cause of death must be comparatively rare, and apparently occurs with no greater frequency than with other drugs in susceptible patients. On the other hand, cutaneous eruptions produced by mercurial diuretics are now probably on an allergic basis, the true mercurial dermatitis being said no longer to occur with the more rapidly excreted mercurials now in use.

The possibility of the nonspecific syndrome of "speed shock" (Hyman[30]) has been considered by a number of authors, but ruled out by most on the basis of the small quantities involved and the time taken for the injection. In reply to this, Hyman points out that the maximum permissible rate of injection will vary depending on the nature of the substance being injected and on the condition of the patient, among other factors. In any case, demonstration of the incoagulability of the blood postmortem would constitute evidence favoring a diagnosis of "speed shock." This was not done in any of the cases mentioned below. Wexler and Ellis[59] maintain that fatal and immediate nonfatal reactions are probably due to the direct toxic effect of mercury on the heart, while delayed nonfatal reac-

tions are incident to the physiologic effects consequent on the diuretic action. Large (and unphysiologic) doses are not always necessary to produce mercurial toxicity: Derow[17] observed a patient in whom the third injection of 2.9 c.c. Salyrgan, making a total of 5.7 c.c., was followed by clinical acute mercury poisoning. The fact that mercury produces pronounced vasodilatation as a result of paralysis of the sympathetic nerves was suggested by Lesser[34] as early as 1888, and was supported, as regards the skin, by the histologic studies of Almkvist.[1]

Lacking, or having no opportunity to obtain, direct confirmation of hypersensitiveness, some authors employ the phrases, "One can only speculate that the reaction is probably an anaphylactic one" (Tyson[55]), or the clinical picture "suggests that the cause of death was an anaphylactoid phenomenon" (Wolf[61]), or the individual "apparently possessed an increased susceptibility to the drug" (Rosenthal[44]), or, "We must assume that this patient possessed a marked degree of susceptibility to the drug" (Andrews[2]). The nature of the evidence favoring an allergic pathogenesis of some reactions, and the possible mechanism of its origin will be considered in the Discussion.

A complete review of all the untoward reactions to mercurial diuretics would be out of place here. Hence only those reports in which an allergic basis was demonstrated, suspected or considered, are included.

FATALITIES

In 1931, Wolf and Bongiorno[61] reported the sudden death of a four-year-old child immediately after his sixth intravenous injection of Salyrgan. Since the previous injection, one week earlier, had been followed by chills, fever and a morbilliform rash, an anaphylactoid phenomenon was thought to be the cause of death. In reporting the autopsy findings of a case dying after the second dose of Salyrgan, Rosenthal[44] suggested that the patient apparently possessed an "increased susceptibility" to the drug, since only a small quantity had been given. Molnár[39] came to the same conclusion in his patient who died twenty minutes after an intraperitoneal injection of 2 c.c. of Novurit (Mercupurin), since the autopsy findings failed to explain the sudden death. Cadbury[12] reported two fatalities and two severe nonfatal reactions from Salyrgan. Two children with nephrosis were observed by Greenwald and Jacobson,[26] each dying one to five minutes after the third injection of Neptal (Salyrgan). Necropsy in one case revealed generalized lymphoid hyperplasia and other findings consistent with an anaphylactoid death. Tyson's[55] case died one minute after the second intravenous injection of Mercupurin in two days, and one of Kline and Seymour's[32] died in convulsions after the second dose of Salyrgan, although one and one-half months had elapsed after the first injection. In the four fatalities reported by Brown et al[10] death occurred within one to four minutes of an intravenous injection of Mercupurin, and was therefore independ-

ent of such factors as massive diuresis, chloride loss or disturbance of electrolyte balance; in three patients, immediate reactions to intravenous injections had been noted prior to the final one. Barker and his coworkers[3] also observed four immediate deaths after intravenous mercurials, including one after an initial dose of Mercupurin, and one after the first dose of Salyrgan (although Mercupurin four months earlier had caused unconsciousness and asystole, followed by short runs of auricular fibrillation). Necropsy findings in each case failed to explain the sudden death.

In a review article in 1942, DeGraff and Nadler[16] accumulated a total of twenty-six deaths attributed to mercurial diuretics reported in the literature over a period of sixteen years. Omitting those patients seriously ill before the injection, Evans and Perry[22] found fifteen instances of sudden deaths in the literature since 1931, and added six cases, four of which had nephrotic syndromes, observed between 1936 and 1943 in the hospitals in one section of London. Although they held the cause of death to be obscure, they stated that it may be an acquired sensitivity. Wexler and Ellis[59] reported two instances of death, each within a few minutes after an intravenous injection of Mercupurin, although the patients had tolerated 164 and thirteen previous injections, respectively. Necropsy revealed no immediate cause of death in either case. Ben-Asher[6] attributed his fatality to extreme hemoconcentration, contributed to by a high environmental temperature, rather than to an allergic mechanism.

CUTANEOUS MANIFESTATIONS

Those cases in which the mercurial sensitivity was manifested as a cutaneous eruption appear, in general, to have been more carefully considered from the allergic standpoint.

The first report of urticaria from mercurial diuretics appears to be that of Turnai,[54] following an earlier reference to the same case by Engel and Epstein.[21] After a number of injections of Salyrgan and Novurit (one of which caused transitory paroxysms), a patient with luetic aortic insufficiency had a pruritic bluish-red papular eruption over the neck and trunk within twenty seconds of a Novurit injection. This was followed by a hemorrhagic urticaria, persisting for five or six weeks, and healing with pigmentation. Salyrgan was tolerated for three months without incident, but a trial of Novurit was again followed by urticaria chronica perstans, as well as by a deleterious effect on the general condition resulting in the death of the patient. Turnai attributed the cutaneous outbreak to an allergic sensitization to Novurit. Urticarial reactions have been also described by Blackford[8] and Kline and Seymour.[32] The former's case, under treatment for congestive heart failure, responded with nausea, headache, vertigo, visual disturbances, pruritus, wheals on the forearms, dyspnea, cyanosis, and vomiting to an injection of 2 c.c.

of Mercupurin and 10 c.c. of aminophylline. A repetition of the injection without the aminophylline was followed by even worse effects. Salyrgan by vein was better tolerated, but still caused symptoms, while a Salyrgan-theophylline rectal suppository produced severe urticaria. Oral tablets of the latter drug were repeatedly tolerated. One of Kline and Seymour's[32] cases had transient urticaria after eight consecutive intravenous injections of Mercupurin, and a diffuse erythematous rash after two subsequent ones, although twenty-two preceding injections of Salyrgan and Mercupurin had caused no untoward effect.

Another of their cases had transient erythema progressing to exfoliative dermatitis with repeated Salyrgan dosage, while a third had a generalized morbilliform rash accompanied by chills, fever, dyspnea, cyanosis, nausea and vomiting after intravenous Mercupurin as well as after Mercurin rectal suppositories. Two additional cases demonstrated no skin manifestations, but were characterized by chills, and by death in convulsions, respectively. While no testing was performed, the fact that one or more intravenous injections had been administered in each case without mishap led the authors to assume that sensitization might be the cause. Although Fox, Gold and Leon's[24] case was known to have urticaria due to hypersensitiveness to a wide variety of foods, her reactions to intravenous Mercupurin and to Mercurin rectal suppositories were not urticarial, but erythematous, at times blotchy in distribution and at other times diffuse. Along with this there were fever, conjunctival congestion, paresthesias, pruritus, numbness of the cheeks and tongue, sensations of substernal constriction and epigastric pressure, salivation, vomiting, swelling of the lips and blurring of vision. Scratch tests with full-strength Mercupurin and Salyrgan were negative. Clinical reactions to Salyrgan or Neptal were very mild, and 196 weekly doses of Salyrgan each containing approximately 80 mg. of mercury, were tolerated. Observation of their case over a period of time revealed the following: as little as 0.1 c.c. of Mercupurin (containing 4 mg. of mercury) produced severe reactions with most of the symptoms mentioned, as did Mercurin rectal suppositories; the reactions were unrelated to massive diuresis, to theophylline and to ionized mercury, such as contained in mercuric chloride or mercuric oxycyanide, and their duration and severity depended on the dose and type of mercurial; and the hypersensitiveness did not seem to change over a period of years. In addition to the sensitivity, symptoms characteristic of mercury poisoning could be produced with larger doses of any mercurial.

Nine cases of erythematous eruptions, all with itching, one being morbilliform in character, were reported by Burrows and Stokes[11] after repeated injections of Neptal (closely related to Salyrgan). In each case, a patch test was positive at the time of, or shortly after, the reaction. Later, in every case, after a brief rest period, the patch test was negative, and at this time intravenous administration of the drug gave no untoward

effects. In one of the earlier reports, Snell and Rowntree[47] described four cases of widespread purpura following injections of Merbaphen. Although these authors dismissed the possibility of an allergic mechanism and attributed the phenomena to the effects of the drug on the capillaries, a number of instances of purpura have been shown to be due to drug allergy (Urbach and Gottlieb[57]). Engel and Marcusson [20] reported two cases with hemorrhagic eruptions and diffuse dermatitis following injections of Salyrgan. Zeiler[62] found the incidence of morbilliform and scarlatiniform rashes to be 0.6 per cent in a series of several thousand injections of Merbaphen to syphilitic patients. Since other mercurials subsequently caused no symptoms, he implicated the complex Merbaphen molecule rather than the mercury itself.

OTHER MANIFESTATIONS

Asthmatic manifestations from mercurials have apparently been reported only twice. Parent[42] observed cough, asthmatic respiration, cyanosis, convulsions, and incontinence after the first dose of Esidrone. The patient recovered and tolerated Mercupurin thereafter, as he had previously. Wexler and Ellis[59] described typical asthmatic attacks with the classical physical findings, occurring one to two hours after Mercupurin administration in two cases. They attribute these reactions indirectly to the diuretic action of the drug, incident to the transitory increase in plasma volume, producing pulmonary edema or bronchial congestion, and resulting in an asthmatic type of respiration in patients with little cardiac reserve. They hold that the mechanism in these two instances was one of a cardiovascular disturbance essentially the same as in the patients who develop pulmonary edema, in which condition, of course, asthmatic breathing may dominate the clinical picture. These authors also reported seven additional cases of alarming nonfatal reactions, chiefly with cardiorespiratory manifestations, including two episodes of pulmonary edema.

Other severe reactions have been blamed on hypersensitiveness. Tyson's[55] case may be considered a "near fatality" with convulsions and coma one minute after an injection of 1 c.c. of Esidrone, although several preceding doses were without these effects. Respiration apparently ceased, and the heart sounds could not be heard. The patient recovered, but only after a period of coma, mania and projectile vomiting lasting for hours. The case observed by Andrews[2] had headache before the completion of the first injection of 0.5 c.c. of Salyrgan, followed in fifteen minutes by loss of consciousness, clonic spasms, marked vasomotor phenomena, and vomiting. In the ensuing twelve hours, five similar episodes occurred. Of ninety-two patients receiving 1,729 injections of Mercuhydrin and Mercupurin, Modell et al[38] noted only two with systemic reactions. In one, faintness and giddiness occurred for thirty minutes after Mercupurin intravenously but not intramuscularly; Mercuhydrin was tolerated. In

the other, chills and fever appeared two hours after Mercuhydrin by either route of administration, but not after Mercupurin.

The following case is thought worthy of description because it is the fourth in the literature in which urticaria was due to a mercurial diuretic and the second in which urticaria was the dominant clinical manifestation; because the hypersensitiveness was proved by skin testing, this being the first such case to be subjected to this proof; because of the successful application of the patch-abrasion or scratch-patch test; and because the test itself was capable of producing a focal reaction in the form of further urticaria.

CASE REPORT

J. A. D., a nineteen-year-old white man, was admitted to the hospital with a diagnosis of nephrotic stage of chronic glomerulonephritis. The past, personal, and family histories were negative for all types of allergic diseases. Physical examination and laboratory study confirmed the diagnosis, with, among other findings, marked dependent edema, ascites, intense albuminuria, and hypoproteinemia. Several intravenous infusions of human serum albumen were tried. When significant clinical improvement did not occur, ammonium chloride was given by mouth, and four injections of Mercupurin* were administered, the first intramuscularly and the subsequent ones intravenously. Adequate diuresis followed each, but the edema never entirely subsided, and fluid reaccumulated each time within a few days. No untoward effects were noted except possibly mild transient headaches, although the patient complained of these at other times as well. The fifth injection of Mercupurin (the fourth intravenous) was given about one week after the preceding one. Approximately seven hours later, the patient was awakened from sleep by generalized itching, most intense in the calves of the legs. Shortly thereafter, a rash appeared in the region of the left shoulder and left thorax, and in the course of the next few hours spread to involve the face and most of the trunk and all extremities. Its appearance was typically urticarial, with raised, pink wheals of roughly rounded outline, except where confluence of the lesions produced gyrate patterns. New wheals appeared and old ones faded at intervals. White blood cell count at this time was 6,600 per cu. mm., with 3 per cent eosinophiles. The temperature rose to maximum of 101.6° F., coinciding with the peak of the rash, and remained between 99° and 100° F. for three days, although it had consistently been normal before. The rash was treated by means of calamine lotion locally, and mild sedation administered. The urticaria faded within about twenty hours, leaving a patchy erythema which persisted for two days. Aside from the intense itching and mild weakness, the patient had no subjective complaints.

Seventeen days later, because of increasing edema, an intravenous injection of 2 c.c. of Mercupurin was again given. Within a few minutes, generalized itching appeared, followed by erythema and general urticaria, along with firm deep swellings of the chin, cheeks, shoulders, and forearms. Epinephrine was administered subcutaneously in divided dosage, but new urticarial wheals continued to appear at irregular intervals, particularly over the upper half of the body, for three days, and during this period the skin was not completely free of urticaria at any time. The temperature was again elevated.

After the subsidence of this episode, skin testing was performed. Patch tests with full strength Mercupurin and Salyrgan-theophylline were negative after forty-eight hours of contact, and when observed after another forty-eight hours. Scratch tests were unsatisfactory, since at the end of twenty minutes the edges of the

*Now known as Mercuzanthin.

scratch seemed acutely inflamed, with intense erythema for a short distance, in both the patient and three control subjects. Mercurial compounds are not suitable for intradermal testing due to their primary irritant nature.

Fig. 1. Reaction of patient to patch-abrasion (scratch-patch) test with undiluted Mercupurin sixteen hours after twenty hours of contact.

TABLE I. REACTION OF PATIENT AND CONTROL SUBJECTS TO MERCURIAL DIURETICS AND AMMONIATED MERCURY OINTMENT

	Mercupurin		Salyrgan-Theophylline		Ammoniated Mercury Ointment, U.S.P.
	Patch Test	Scratch-Patch Test	Patch Test	Scratch-Patch Test	Patch Test
Patient, J. A. D.	neg.	str. pos.	neg.	wk. pos.	neg.
P. E. K. (allergic)	neg.	neg.	neg.	neg.	neg.
S. G.	neg.	neg.	neg.	neg.	neg.
A. B.	neg.	neg.	neg.	neg.	neg.
B. H. D.	neg.	neg.	neg.	pos.	neg.

Hence a patch-abrasion or scratch-patch test (Tucker and Thomas[53]) was performed. For this purpose, after cleansing of the skin, three or four superficial scratches were made in a crosshatch pattern on the skin of the forearm, insufficient to draw blood. Over this was placed a square of white blotting paper approximately 1 cm. square, saturated with undiluted Mercupurin solution. About two hours later, the patient complained of generalized itching, and soon thereafter noted urticarial wheals over the arms (including the region adjacent to the test), anterior chest, upper back, and face. This outbreak was similar to his previous episodes except that it was not generalized and that the individual wheals were possibly somewhat smaller. These symptoms were not made known until the test was read, when the hives were beginning to fade. The patch was removed at the end of twenty hours, at which time the entire test area was the site of sharply demarcated swelling of a firm consistency, along with moderate erythema. Observed daily, these changes persisted with gradually increasing intensity for another forty-eight hours, then declined gradually. A photograph of the reaction was taken thirty-six hours after the application of the drug, or sixteen hours after the removal of the patch (see Fig. 1). The patient was tested similarly with injectable Salyrgan-theophylline and had a similar reaction although less intense, persisting for three days.

In order to confirm the specificity of the reaction, four control subjects, one

with allergic bronchial asthma and three with various diseases, were tested by the same techniques. The results are shown in Table I. The negative scratch-patch tests revealed only barely discernible lacerations at the sites of the tests at the time of the removal of the patches, and even this was gone in a day or two. The reaction of patient B.H.D. to Salyrgan may be commented upon. This man, with hypertensive heart disease in congestive failure, had had three injections of Salyrgan-theophylline previously, and had a number subsequently, all without untoward incident. The significance of the positive skin test in this case is not known.

DISCUSSION

There can be no doubt, in view of the time relationships involved, that the urticarial eruptions in this case were due to the injected Mercupurin. The patient had never previously suffered from urticaria. He was also fed, in as nearly the same quantity and same method of preparation as possible, those foods which he had taken before the appearance of the rash. No reaction occurred. An allergic mechanism is proved by the positive response to the patch-abrasion test, and even more decisively by the focal or urticarial reaction to this test. While the actual patch used in the test was discarded, comparable ones prepared from the same material were found to hold, at most, less than 0.1 c.c. of Mercupurin solution (containing 4 mg. of mercury). While it is not possible to determine how much of this was absorbed, the quantity must have been quite small, and yet it was capable of causing a fairly extensive urticaria. It is inconceivable that such an amount could produce its effects either by direct toxic action of the mercury or by its effects on blood volume, diuresis (which did not ensue), electrolyte or water balance.

The negativity of the patch test is not surprising, since epidermal sensitivity is not anticipated. Scratch testing was unsatisfactory. However, the scratch-patch test proved to be of value in confirming the allergic nature of the case. This method of testing was successfully employed recently with such drugs as sulfanilamide (Fisher[23]) and penicillin (Urbach and Gottlieb,[57] O'Donovan and Klorfajn[41]). This technique should probably be employed more extensively in instances of suspected drug allergy, in order to define more precisely its limitations and the control of the variables involved.

It is beyond the scope of this paper to discuss the advisability of employing mercurial diuretics in the presence of demonstrable renal disease. Opinions apparently differ on this point. However, a considerable proportion of the reported untoward reactions occurred in patients with nephrosis or nephritis, although it is likely that these drugs are used far more frequently in cases of cardiovascular disease. Tyson,[55] Evans and Perry,[22] and others suspect that this may be connected in some way with the altered blood proteins present in the former patients, with decreased total blood protein values, an actual or relative reversal of the albumin-globulin ratio, and perhaps even a change in the quality of the protein. While no fatalities have been reported after the intramuscular injection of a mercurial diuretic, and while some authors have recommended that

injections of mercurial diuretics, in cases of nephritis and possibly other diseases associated with low plasma protein levels, be restricted to the intramuscular route in order to prevent severe reactions, experience with this avenue of administration has not been sufficient to know whether this precaution will be effective. It has even been recommended that the susceptibility of the patient be tried first by means of two or three intramuscular doses in increasing quantity before trying intravenous injections.

However, Greenwald and Jacobson[26] suggested that the first intramuscular injections may actually be responsible for sensitization, while a change to the intravenous route may cause shock in human beings. Chastain and Mackie[14] were unable to confirm this hypothesis in experiments on dogs, but the well-recognized difficulties of allergizing animals to drugs vitiates the applicability of this work as regards clinical experience.

It is apparent that only a very small percentage of serious untoward reactions have occurred after the first injection of a mercurial (Andrews,[2] Cadbury,[12] Barker et al,[3] Sundaram[50]), the vast majority appearing after the third or subsequent administration. This, of course, constitutes a point of indirect evidence favoring a mechanism of allergization as the cause. Equally important, however, is the conclusion that physicians should be forewarned not to neglect the possibility of an untoward reaction merely because previous injections were tolerated without incident. Also, in a number of reported cases, minor reactions, chiefly cutaneous in nature, but also chills and fever and transitory cardiac arrhythmias, preceded the ultimate serious or fatal reactions. Such danger signals should constitute a warning of possible sensitization, a basis for careful review of the therapy of the individual case and, in all probability, a strong indication for the discontinuance of mercurial drugs.

A review of the reported instances of suspected sensitivity to mercurial diuretics reveals the extreme paucity of skin tests. Of course, the cases ending fatally gave no opportunity, although some of them had immediate nonfatal reactions preceding the fatal one. Had these been tested at this time, it is possible that valuable information might have been gained. It is thought that cutaneous eruptions produced by mercurial diuretics in recent years are probably allergic in character rather than on the basis of a true mercurial dermatitis, which is said not to occur since the employment of the more rapidly excreted theophylline-containing mercurials. The positive patch tests uniformly obtained by Burrows and Stokes[11] are of particular interest, but it must be recalled that they dealt exclusively with instances of erythematous skin eruptions. The reversal of the patch tests after a short rest period (without hyposensitization) and the concomitant tolerance of the drug is rather unlike the usual experience with drug allergy, and in direct contrast to the findings of Fox, Gold and Leon,[24] whose patient's hypersensitiveness did not seem to change over a period of years. Their clinical observations led Burrows

and Stokes[11] to conclude that a failure of diuretic response to continued frequent injections of mercurials appeared to enhance accumulation of the metal and subsequent cutaneous sensitization. Such cumulative effects seemed to depend on too high or too frequent dosage, renal impairment, congestive changes, prolonged administration, and especially deficient elimination of the drug (i.e., poor diuresis). Obviously, this explanation does not apply to the majority of cases. Nevertheless, they believe patch testing to be useful when accumulation of the drug is suspected or when continuation of the therapy is desirable after cutaneous sensitization to mercury, and that the latter need not contraindicate the subsequent employment of these diuretics in adjusted dosage after a short interval. With this conclusion most authorities disagree,[18] and certainly in the case reported herein, a rest period of seventeen days not only failed to prevent symptoms, but was actually followed by a more severe and more promptly appearing reaction. The marked shortening of the latent period between the administration of the drug and the appearance of urticaria on the two occasions is worthy of note. It seems safe to conclude that the occurrence of even mild reactions in the course of treatment should be considered a contraindication to further exhibition of these drugs. Such a precaution would have prevented a number of the reported fatalities.

Hyposensitization to mercurial diuretics has not been reported. None of the reported cases, except the present one, appears to have been treated by antiallergic measures.

Two other suggestions have been advanced to prevent untoward incidents, viz., a change in the mercurial diuretic employed, and a change in the route of administration. Without going into detail on these points, it may be stated that while some patients sensitive to one mercurial may tolerate another with impunity (e.g., Fox et al,[24] Modell et al,[38] Turnai,[54] Parent[42]), in many cases this will not be true (Blackford,[8] Barker,[3] Wexler and Ellis[59]). In the former type, the hypersensitiveness would appear to be related to the organic structure of the drug; in the latter, to the mercury itself. In the case reported here, it should be noted that a scratch-patch test with Salyrgan-theophylline was positive, although the drug itself was not administered. According to Wexler and Ellis,[59] there is no indication that changing from one preparation to another is a safeguard against fatal reactions. Likewise, changing the route of administration to the intramuscular or rectal, while sometimes effective, will by no means always prevent reactions (Blackford,[8] Kline and Seymour,[32] DeGraff and Nadler,[16] Barker et al,[3] Brown et al,[10] Fox et al,[24] Modell et al[38]). This statement seems to be particularly true of those patients who have shown definite allergic reactions, such as urticaria, rash and fever. There is no reason to think that diluting the drug with physiologic solution of sodium chloride prior to injection, as has sometimes been done, will in any way reduce the incidence of untoward episodes.

It seems likely that reactions occurring promptly after administration of the drug are based on one of three possible mechanisms: allergy, toxicity, and "speed shock." In many instances (Wolf and Bongiorno,[61] Greenwald and Jacobson,[26] Tyson,[55] Barker[3] and Brown,[10] among others), the untoward reactions and even fatalities occurred within one or two minutes after the injections. In such cases, attempts to attribute the untoward action to the physiologic effects of the drug incident to the diuresis, with the ensuing alterations in plasma volume, electrolyte and water balance, would seem to be disproved by the very rapidity of the reaction. Wexler and Ellis[59] hold that the asthmatic manifestations which they observed in two cases were accounted for by pulmonary edema or bronchial congestion in patients with a low cardiac reserve. However, while no final statement can be made, the facts that the attacks appeared in one or two hours, that they occurred only after the last of several injections, that relief was afforded in one case by epinephrine and that asthma is so frequently a symptom of hypersensitiveness, make an allergic basis for these findings at least equally plausible. Unfortunately, no testing was done. Primary toxic action of the mercury may be ruled out in many cases by a consideration of the total dosage received and by the clinical (or necropsy) findings. "Speed shock" would appear to depend largely on the rate (and quantity) of intravenous injection, but could be confirmed, even after death, by following a suggestion by Hyman.[30] Since the freshly drawn blood is rendered incoagulable by "speed shock," it would be well to make this simple observation in cases of these unfortunate therapeutic accidents.

Thus, there remains the allergic explanation. The fact that most reactions and most fatalities occurred after a series of injections with mercurial diuretics would lend support to this concept. Other evidence favoring this mechanism has been discussed above.

Finally, the possibility that mercury in these diuretics may act as a hapten remains to be considered. Haxthausen[28] showed that mercury, as well as other simple chemical compounds, is sometimes capable of producing cutaneous hypersensitiveness of eczematoid character in human beings in certain concentrations only after conjugation with foreign protein—among other substances, animal serum. It has already been noted that many of the untoward reactions, including that here described, occurred in patients with lowered plasma protein levels and abnormal albumin-globulin ratios resulting from the underlying disease. Greenwald and Jacobson,[26] Tyson,[55] and Evans and Perry[22] favor the concept that the mercury functions as a hapten, conjugation possibly taking place more readily with a lowered or altered plasma protein.

SUMMARY AND CONCLUSIONS

Mercurial diuretics may act as allergens, giving rise to a considerable variety of clinical manifestations and even fatalities. However, these

potent drugs may also produce untoward reactions by any one of several other mechanisms, of which may be mentioned primary toxicity of the mercury, especially on the heart, disturbances of plasma volume and fluid balance, electrolyte imbalance, "speed shock," overdigitalization and renal complications. Hence, it is incumbent upon the physician to study each such case as carefully as possible in an effort to determine the cause. From the allergic standpoint, patch-abrasion and patch tests would appear to be the most informative.

Fortunately, the over-all incidence of untoward reactions to these valuable drugs appears to be low. A reliable method of predicting untoward or fatal reactions in human beings is not available.

A case is reported in which generalized urticaria followed the fifth and sixth injections of Mercupurin, being the second case in the literature in which urticaria was the dominant clinical manifestation of hypersensitiveness to a mercurial diuretic.

The etiology of the eruption was confirmed by a positive patch-abrasion (scratch-patch test). The minute amount of the drug absorbed from the test site evoked a focal reaction in the form of further urticaria. The value of this method of testing is emphasized. It is recommended that the scratch-patch test be more extensively employed in suspected drug allergy.

Hypersensitiveness to mercurial diuretics is most likely to be manifest by cutaneous eruptions, but there is reason to suspect that chills and fever, asthmatic syndromes, convulsions, and death may occur on an allergic basis. The more serious reactions are not infrequently preceded by minor episodes, chiefly cutaneous, and these should constitute a contraindication to further mercurial therapy.

Allergic reactions are more likely to occur on multiple injection (usually after more than two), in patients with the nephrotic syndrome, with lowered plasma protein values and abnormal albumin-globulin ratios. A hapten mechanism is plausible.

Once an untoward, and particularly an allergic, reaction to a mercurial diuretic has occurred, the following, although sometimes effective, cannot be depended upon to prevent further episodes: a change in the drug employed, a change in the route of administration, or allowing a "rest" period. Dilution of the drug with physiologic saline solution has proved ineffectual for avoiding such effects.

The clinical features, recognition, and mechanism of hypersensitiveness to mercurial diuretics are discussed.

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A COMPARATIVE STUDY OF COMMERCIAL NEBULIZERS

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NUMEROUS asthmatic patients during the past decade have stated, in giving their history, that they have tried inhalation of nebulized ephinephrine solution without relief, even in attacks of mild to moderate severity. Investigation invariably revealed that they had used a defective nebulizer or one of inadequate design. Some had tried several types and usually attributed success or failure with a certain model to the solution used rather than to the instrument. Matzger,[14] in 1935, stated that "a considerable quantity of vapor without droplets must be produced," and Graeser,[13] in 1939, reported "failure of the procedure in many instances is due to an inefficient atomizer."

Very little information is to be found regarding the characteristics of the various nebulizers commercially available. The Council on Physical Medicine has examined and accepted only three, the DeVilbiss Nos. 40 and 44[10] and the Holmspray No. 630.[11] Richards, Barach and Cromwell[16] found both the Vapco and the Vaponefrin models satisfactory, stating that the Vaponefrin produced a somewhat more voluminous stream. Stacey[17] used the DeVilbiss No. 40 and the Parke-Davis Adrenalin Vaporizer for nebulization of sulfonamide solutions but made no comment as to their efficiency. Abramson[2,3] has mentioned the DeVilbiss No. 40, the Vaponefrin, the Asthmamist, and the Ailene as being satisfactory, and states that the unpublished data of Bryson indicates that the particle size distribution of the first three is approximately the same. He stated that the particle radii in these models vary from 0.3 to 2 microns, not counting a certain amount of "rain" due to imperfect construction. In another paper[4] Abramson states that 50 per cent glycerol formed stable mists with the DeVilbiss No. 40, the Vaponefrin, and the Parke-Davis table model. The mist from the DeVilbiss No. 40 contained particles with diameters as follows: below 2 microns, 7.2 per cent; 2 to 6 microns, 65.5 per cent; 6 to 8 microns, 18 per cent; 8 to 38 microns, 9.4 per cent. These figures are at variance with those of Bryson, probably because, as Abramson states, this method yields a preponderance of larger droplets. Presumably the percentages refer to numbers rather than total mass of droplets in each group. Bryson, Sansome, and Laskin[6] give the average particle radius of the DeVilbiss No. 40 as 0.54 microns, with a range of 0.24 to 1.18. Barach et al[5] state that the Vaponefrin model delivers a majority of particles under 1 micron—whether diameter or radius is not stated. Only a negligible amount of medicament is returned in the expired air. Castex et al[8] used a nebulizer of their own design which was presumably satisfactory. Mutch[15] found the Collinson nebulizer satisfactory.

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It was felt that it would be of service to acquaint the medical profession with certain details of the performance of the various models of nebulizers on the market. Since nebulizers are at present being put to a variety of uses, no one type is likely to be best for all purposes, although, as will be seen, some are capable of modification to increase their versatility.

Complete or partial failure of a given model could be due to (1) the production of an insufficient amount of mist, (2) too many large particles which do not get beyond the mouth and pharynx, and/or (3) a preponderance of actual vapor or of particles so small that they are exhaled. This latter effect may be due, in part, not to the nebulizer itself, but to the use of a solution which contains an insufficient amount of substances which lower the vapor pressure and thus enhance the permanence of the mist. The reduction in size of aqueous particles after they are generated is influenced by the temperature and relative humidity of the surrounding air. Mutch[15] states that the life of an aqueous particle of 2 microns diameter in dry air is only 0.0006 seconds. It obviously takes far longer than that for a particle to travel from the tip of the jet to a point in the respiratory tract where the relative humidity is 100 per cent. Even a glycerin particle does not last long in dry air although it may actually grow in moist air. It should be noted also that particles which lodge in the alveolar ducts and sacs have no local effect in relieving bronchospasm and are effective only as they are absorbed into the blood stream. According to Findeisen,[12] 84 per cent of particles of 2 microns in diameter, are deposited in these locations.

PROCEDURE

Nebulizers containing small amounts of distilled water were weighed before and after 500 compressions of the hand bulb, and the weight delivered by one squeeze of the bulb was calculated. The averages for the samples of each brand tested are shown in Table I. The variation among models of the same brand will be discussed later. The results are naturally influenced by the volume of the hand bulb. The capacity of the bulb supplied with each model is shown in the table. For the nebulization of solutions by pressure from an oxygen tank or by compressed air, the time required to nebulize 1 c.c. of water is more pertinent. The values obtained by oxygen pressure with the flowmeter set at 8 liters per minute are shown in the table. Also shown are values obtained with a small air compressor, manufactured for the purpose by the Selrodo Company and said by the company to generate 40 pounds pressure per square inch.

A few samples tested delivered visible droplets. This is recorded in the table. If the amount was not sufficient to be considered important, a 1-plus is recorded. Amounts of more serious proportions are appropriately indicated.

Accurate measurement of particle sizes in a mist is a difficult technical procedure. Furthermore, the size of the particles generated will vary with

TABLE I. COMPARISON OF COMMERCIAL NEBULIZERS

No.	Model	Number Tested	Mg. in One Puff	Capacity of Bulb c.c.	Seconds to Nebulize 1 c.c. H_2O		Radius of Particles (Microns)**		Droplets
					O_2 at 8 l/min.	Comp. Air	Median	Largest	
1	Breatheasy	2	13.0	76	35	31	15	175	0
	Breatheasy No. 2		7.9	49	31	30	19	250	0
	No. 1 with L-tube	1	7.2		72	68	13	78	0
	No. 1 with carburetor closed	1	3.0		182	155			0
2	Asthma Nefrin	3	2.84	65	101	98	8	212	++(1) +(1)
	best with L-tube		3.0		100	137	10	80	0
3	Vaponefrin	6	2.1	65	194	169	16	127	0
4	Pen-i-sol	2	1.7			350			0
5	DeVilbiss 40	6	1.6	61	225	187	13	132	+(1)
	best with L-tube		1.3		230	200	15	60	0
6	Vapco*	6	1.52	76	287	239	29	150	+(1)
7	Broemmel	4	1.42	61	273	235	21	207	0
8	Peralta*	3	1.4	61	317	195	17	308	+(2)
9	Selrodo*	2	0.96	39	300	235	11	125	0
10	Endiphrinizer*	1	0.86		705	300	18	100	+
11	Parke-Davis "Nebulizer"*	3	0.82	67	480 (1)	drops	11	325	++(3)
12	DeVilbiss 44*								
	old type	2	0.60	59	drops	drops	10	40	0
	new type	2	0.77	61	634	432	19	75	0
13	Defender*	2	0.73	60	660	445 drops(1)	12	150	++(1)
14	Stearns* old type	4	0.68	47	472	367	11	87	0
	new type	2		67	575	drops	12	175	+++(2)
15	Parke-Davis "Vaporizer"*	5	0.40	60	608	450 drops(2)	10	165	++(2)

* No carburetor hole.
** Values have comparative significance only.

the room temperature, the force of the blast and the viscosity and surface tension of the liquid. A number of factors will also change the size of the particles from the time they are generated until they are deposited on the respiratory mucosa. Factors which increase particle size are (1) collision of particles with each other in areas of turbulence, or by large ones overtaking the smaller; and (2) hygroscopy, if the solution has that property. Particle size may be diminished by evaporation. As previously stated, this is a function of the temperature, the relative humidity, the vapor tension of the solution, and the diameter and velocity of the particle.

After considerable experimentation with different solutions and different methods of collecting and visualizing the mist particles, the following simple technique was adopted. A small quantity of 1 per cent aqueous gentian violet solution was placed in the nebulizer and the mist sprayed against a clean glass slide held exactly one-half inch from the mouthpiece of the nebulizer. The size of the colored circular spots was then determined, using an ocular micrometer in the microscope. The median size obtained with the samples of each model was determined and the mean for the model recorded in the table. The largest droplet found with each sample was also measured and the mean for the samples for each model entered in the table. *It should be emphasized that these values have comparative significance only.* The absolute sizes are probably quite different. Many of the smaller particles evaporate before they reach the

glass slide, or drift away without adhering to it. Also we cannot determine the size of the original spherical particle from the size of the flat circular spot left on the slide. A considerable amount of flattening must occur, and this amount will depend upon the momentum and size of the particle. The factors previously mentioned which tend to alter the size of the particle from the time it is generated are also operative. It should be remembered that the amount of medicament carried by particles of different sizes varies with the cubes of their radii. For example, if 99.9 per cent of the particles of a mist were 1 micron in radius and 0.1 per cent were 10 microns in radius, the mass of medicament would be equally divided between the two sizes.

DISCUSSION

As is shown in the table, the amount of solution delivered by one compression of the hand bulb varies in the different models from 0.4 mg. to 13.0 mg. If individual samples are considered, the difference is even greater. It is therefore not a matter of indifference which model is selected. Merely to increase the number of inhalations when using the less efficient models is often not satisfactory. Even with efficient samples, many chronic asthmatics develop thick calluses on their hands from squeezing the bulb. The original workers who investigated inhalation of nebulized epinephrine in asthma quickly found that ordinary atomizers which sprayed droplets were unsatisfactory. A DeVilbiss No. 14 atomizer delivers about 100 mg. of the solution, mostly in the form of droplets, with one squeeze of the bulb, and deposits the bulk of the solution in the mouth, pharynx, and trachea. It would seem to the writer that the designers of some models of nebulizers have gone too far in trying to eliminate droplets from the spray. They have provided baffles which take out too much of the spray and in some cases, by inadequate streamlining of the instruments, have created areas of turbulence which defeat the purpose of a baffle, so that particles are actually enlarged by collision with each other. Also, to minimize clogging, they have made the capillary tube which delivers the air blast too large. This necessitates a quick, vigorous squeeze of the bulb and results in a very brief stream of mist. A more prolonged stream is a distinct advantage.

The models which deliver the greater amount of mist are preferable in nebulization of antibiotics because they reduce the time necessary for the patient to inhale the medicament. When used for this purpose, the production of droplets is not so serious as when used for inhalation of epinephrine.

By the method used in this study, no conclusion can be drawn regarding the effect of particle size on clinical efficiency. For example, two very efficient models, the Asthma Nefrin and the Vapco, are at the opposite extremes so far as the median size of the particles is concerned. It may very well be that if we could determine the percentage of medicament which is

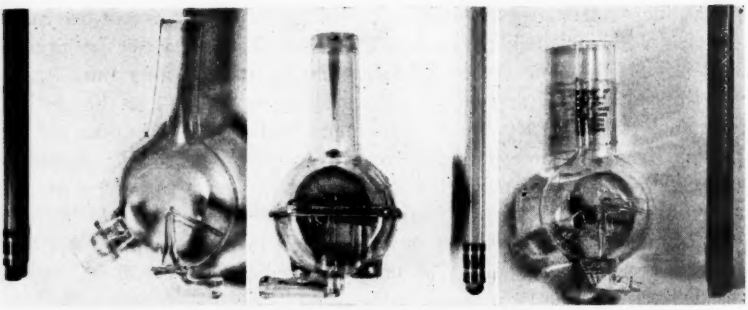

Fig. 3. Vaponefrin. Fig. 2. Asthma Nefrin. Fig. 1. Breatheasy.

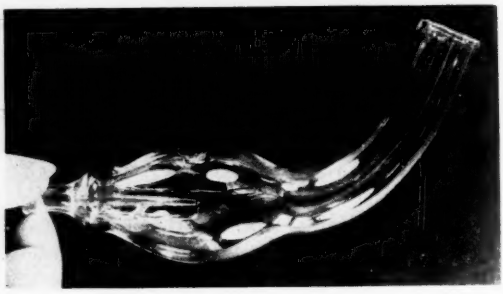

Fig. 4. DeVilbiss No. 40.

carried by the smaller particles and exhaled, we could better explain success and failure with certain nebulizers. Also if we knew the percentage by weight of particles which are deposited in the alveoli we could better choose which nebulizers to use for local effect on the bronchi and which to use when systemic absorption is desired.

NEBULIZER MODELS

1. *Breatheasy* (Breatheasy Distributors, Inc., 65 Cedar Street, Seattle 1, Wash. Pyrex. $10.00). As defined by Abramson,[3] instruments without baffles are atomizers. Technically, according to that definition, this model is, in part, an atomizer, since some of the mist stream passes in a straight line from the jet to the mouthpiece. However, particle sizes compare favorably with other models. The stream of mist is emitted with considerable velocity so that the larger particles lodge on the posterior pharyngeal wall (many particles were deposited on a mirror one foot away from the mouthpiece). The large volume of mist delivered may be objectionable in the hands of children and uncooperative patients. The amount of mist and the velocity of the particles may be sharply diminished by closing the carburetor hole. The larger particles may be removed nicely by the use of an L-tube such as is supplied in the DeVilbiss No. 640

combination. The Breatheasy model would seem to be the instrument of choice for such procedures as local administration of streptomycin in tuberculous laryngotracheitis. The variation in the performance of the two samples listed is chiefly due to the different capacities of the hand bulbs

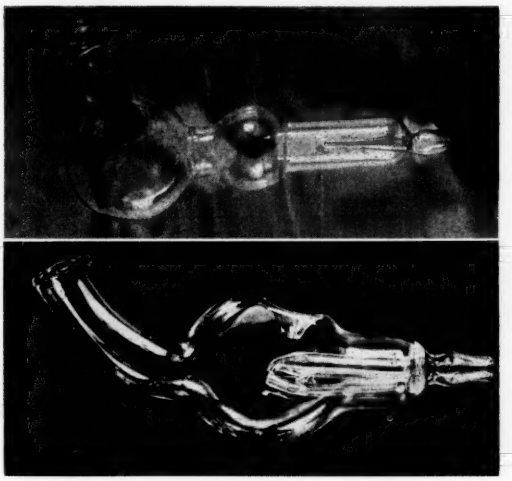

Fig. 5. Vapco.
Fig. 6. Broemmel.

supplied "as purchased." Two additional samples with the larger bulb yielded 7.0 mg. and 14.3 mg., respectively, with one compression. I have had too little experience with this model to report on clinical results with it. It gives a desirably prolonged stream with each blast.

2. *Asthma Nefrin* (Asthma Nefrin Co., 3146 E. Burnside St., Portland 15, Oregon. Plastic. $10.00). There was little variation in the samples tested. It is very similar in design to the Vaponefrin model. It is somewhat more difficult to clean than are the glass nebulizers.

3. *Vaponefrin* (Vaponefrin Co., Upper Darby, Pa. Pyrex. $7.50). Output in the six samples tested varied from 1.36 mg. to 2.72 mg. in one puff. Very good clinical results have been widely reported.[2,3,5,16] The vapor stream is gratifyingly prolonged.

4. *Pen-i-sol.* This is sold for inhalation therapy with antibiotics, not for epinephrine therapy.

5. *DeVilbiss No. 40* (DeVilbiss Co., Toledo, Ohio, $2.50). The output varied from 1.2 mg. to 1.84 mg. in one puff. Good clinical results have been reported.[2,3,4,6]

6. *Vapco* (Vaporizer Products Co., 776 Harrison St., San Francisco 7, Calif. $2.75). The output varied from 1.12 mg. to 1.68 mg. in one puff. A fine, billowy cloud of mist is produced. This is the most efficient of

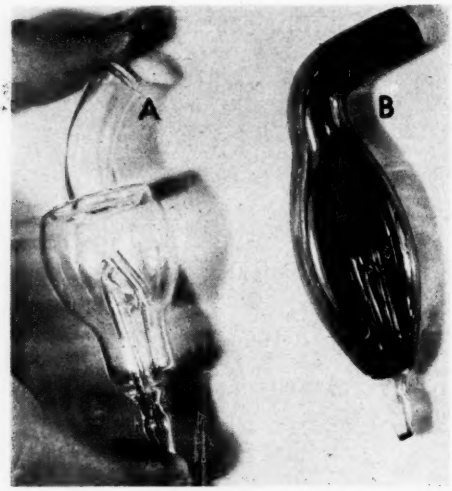

Fig. 7. (A) Peralta. (B) Selrodo.

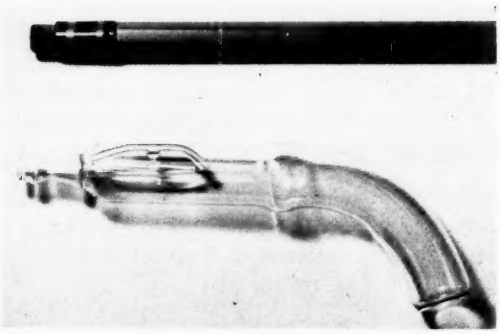

Fig. 8. Endiphrinizer.

the models tested which have no carburetor hole; and of those which have a carburetor hole, only the Breatheasy exceeds it when operated with the hole closed. The rather large median size of the particles should be advantageous in medicating the upper part of the bronchial tree. Asthmatic patients report good results with this nebulizer.

7. *Broemmel* (Broemmels Pharmaceuticals, 384 Post Street, San Francisco, Calif. $4.50). This is a very compact nebulizer. It produces a fine

cloud of mist. The output in four samples varied from 1.42 mg. to 1.6 mg. in one puff. It gives a prolonged vapor stream. To shorten the time in the inhalation of antibiotics, et cetera, a Y-tube may be connected to the

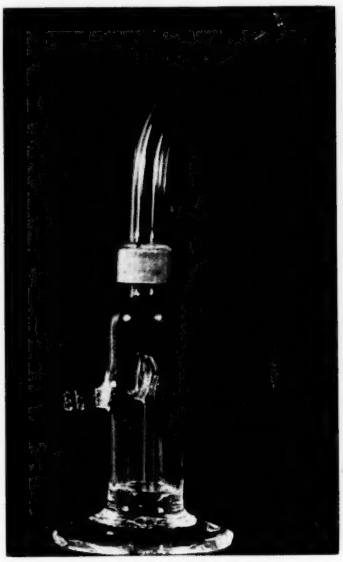

Fig. 9. Parke, Davis "Nebulizer."

tube from the oxygen tank and a pair of these nebulizers, held together by tape, may be attached to the two forks of the Y-tube.

8. *Peralta* (Peralta Hospital, Inc., 430 30th St., Oakland, Calif. Pyrex. $2.50). The output varied from 0.8 mg. to 2.4 mg. in the four samples tested. It is constructed with a "moat" so that it will not spill if laid down. I have had too little experience with this model to report results.

9. *Selrodo* (Stansbury Chemical Co., 1929 Aurora Ave., Seattle 9, Washington. Brown glass. $5.00). (Formerly Halomist, 705 Shafer Building, Seattle, Washington.) This was the most compact model examined. The output varied from 0.8 mg. to 1.12 mg. in one puff in four samples. Patients report good results with this model. A pair may be used as described with the Broemmel. I would prefer a larger hand bulb.

10. *Endiphrinizer* (The Harrower Laboratory, Inc., Glendale, Calif. $1.50). Only one model was tested, and I have had no clinical experience with it.

11. *Parke-Davis "Nebulizer"* (Parke, Davis & Co., Detroit, Mich. $1.50). The output varied from 0.68 to 1.0 mg. in one puff in three

samples. Too many droplets were produced in the samples tested. Only one of the three could be used with oxygen at 8 liters per minute and none with the Selrodo air compressor. It might be improved by providing a mouthpiece of larger diameter.

Fig. 10. (A) Defender. (B) DeVilbiss No. 44.

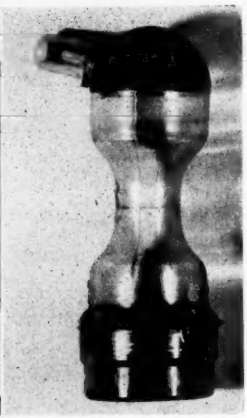

Fig. 11. Stearns.

12. *DeVilbiss No. 44* (DeVilbiss Company, Toledo, Ohio, $1.50). The output of two old type models was 0.44 mg. and 0.76 mg., respectively, in one puff. The old type could not be used with oxygen at 8 liters per minute, or with the Selrodo compressor, due to emission of drops. The new type has a mouthpiece of larger diameter and was satisfactory in this respect. The output of the two new models was 0.7 mg. and 0.84 mg., respectively, in one puff.

13. *Defender* (United Drug Company [Rexal] $1.50). This model appears to be similar to, if not identical with, the Holmspray No. 630, judging from an illustration of the latter only. The output was 0.69 mg. and 0.86 mg. per puff in the two samples. One sample emitted droplets. I have had no clinical experience with this model.

14. *Stearns* (Frederick Stearns & Co., Detroit 31, Mich. Plastic. $1.50). In addition to hand bulb operation, this model has three inlet holes in the base which permit the patient to use the instrument without a bulb by inhaling forcibly through the mouthpiece. These holes also act as "carburetors." This method is usually effective only in mild attacks of asthma. The old type had a curved baffle plate in the dome and emitted a fine mist. The new type has no baffle plate. Furthermore, the mouthpiece tube projects into the dome and has a beveled end with the bevel turned downward so that in the two samples tested, droplets were emitted. In

the author's opinion, this model was improved when he substituted a mouthpiece of larger diameter, attached flush with the wall of the dome, and bored a ⅛ inch carburetor hole in the side.

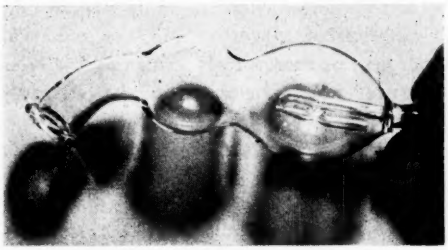

Fig. 12. Parke, Davis "Adrenalin Vaporizer."

15. *Parke-Davis Adrenalin Vaporizer* (Parke, Davis & Co., Detroit, Mich. $1.50). The output varied from 0.36 mg. to 0.46 mg. in one puff. It produces an almost invisible mist. The vapor stream is very brief. Two of five models emitted droplets with the hand bulb and could not be used with the Selrodo compressor. Failure to relieve asthma was very frequently reported with this model. In justice, it should be stated that this may be due in part to the probability that it outsells all others.

SOLUTIONS

Abramson,[1] in 1940, pointed out the advantage of adding to the solution to be nebulized some substance which lowers the vapor pressure. Glycerin was found to be the most satisfactory for this purpose. Concentrations of 10 to 50 per cent were used but 50 per cent was the concentration of choice. In a later communication[2] he lists the advantages of adding glycerin, as (1) stabilization of the mist, (2) reduction of irritation, and (3) retardation of absorption.

So far as is known to the author, only two commercial solutions and the solution adopted by the U. S. Army for the inhalation of epinephrine contain glycerin, as will be seen later.

The viscosity of aqueous solutions containing glycerin increases geometrically as the percentage of glycerin increases. Because of this increase in viscosity it is desirable to keep the percentage of glycerin at the lowest point which will accomplish stabilization of the mist. Examples of the viscosity of aqueous solutions of glycerin at 20° C. follow:

Glycerin %	Viscosity
10	1.3
25	2.1
35	3.0
50	6.0
67	18.0
75	36.5
95	540.0

For those nebulizers which produce an adequate volume of mist with distilled water, the reduction in volume when 50 per cent glycerin was substituted was not serious. Indeed, with most of them, 75 per cent glycerin could be used satisfactorily.

In addition to the advantages enumerated by Abramson, there are other reasons for the addition of glycerin: (1) the remarkable chemostatic properties of 50 per cent or more of glycerin, (2) bacteriostasis in similar concentrations, (3) prevention of clogging of the jet, and (4) the wetting effect.

Allergists are well aware that allergen extracts remain sterile and potent almost indefinitely in 50 per cent glycerin. Enzymes likewise retain their potency for prolonged periods in this medium. It seems probable that the result would be similar with antibiotics. If this is so, then even though glycerin is not necessary to stabilize penicillin mists, because of the stabilizing effect of the penicillin itself, the addition of 50 per cent glycerin would seem desirable since it would make refrigeration unnecessary.

Clogging of the jet of the nebulizer is usually due to the deposition of solid particles as the water itself evaporates. This characteristic is especially important in the nebulization of sulfonamide solutions in which 5 per cent is the usual concentration of the drug. Glycerin, since it is nonvolatile, prevents this effect.

The formulas of some commercial and noncommercial epinephrine solutions, with comments, follow:

Breatheasy

Racemic epinephrine HCl	3%
Benzyl alcohol	1%
Vanillin	0.2%
Sodium chloride	0.9%

The dextro-isomer of epinephrine is relatively inert. Two per cent racemic epinephrine is about 7 per cent more active than 1 per cent U.S.P. (levo-)[1] epinephrine. Therefore this solution is approximately equivalent to 1.6 per cent U.S.P. The benzyl alcohol is added for its local anesthetic properties and the vanillin for chemostabilization. Some patients like the strong vanilla odor, others object to it. The addition of 0.9 per cent sodium chloride to a solution containing the other diffusable ingredients makes this solution hypertonic.

Vaponefrin

Racemic epinephrine HCl	2.25%
"analogous to 1.5% U.S.P."	
Chlorobutanol	0.5 %

This solution is sold only through physicians. Essentially identical solutions are sold directly to the public under the names of Asthmanefrin, Solution A, Inhalant A, Neosol, Solution N, and Inhalant N.[1]

Epinephrine inhalant

Epinephrine (Vaporizer Products Co.)	1.0%
Chlorobutanol	0.5%
Sodium chloride	0.8%
Sodium bisulfite	0.1%
Glycerol q. s.	
Aqua destillata q. s.	

Adrenalin chloride (Parke, Davis & Company) 1:100

Adrenalin HCl	1.0%
Sodium chloride	0.9%
Chloretone	0.5%
Sodium bisulfite	0.1%

Suprel (formerly Nebulin A) (Frederick Stearns & Co.)

Epinephrine HCl	1.0%
Alcohol	0.5%
Glycerine	7.5%
Chlorobutanol	0.5%
Sodium bisulfite	0.1%

Endiphrin Inhalant (Harrower Laboratory)

Epinephrine HCl	1.0%
Sodium chloride	0.9%

Selrodo (formerly Halomist)

Racemic epinephrine "approximately equivalent to 0.9% U.S.P."	1.8%
Chlorobutanol	0.9%

"Selrodo" spelled backwards is "odorles," but the odor of chlorobutanol is readily detectible.

U. S. Army, Stock No. 1,175,320, July 16, 1945

Epinephrine HCl	1.0%
Sodium chloride	0.9%
Glycerin	25.0%
"Suitable preservatives"	
Water q.s.	100.0%

Typical formulas used by Abramson:

1.	Epinephrine HCl	1.0%
	Chloretone	0.5%
	Sodium bisulfite	0.1%
	Water	50.0%
	Glycerine	50.0%
2.	Epinephrine base	1.0%
	Chloretone	0.5%
	Sodium bisulfite	0.1%
	Water	40.0%
	Molar phosphoric acid	5.2%
	Glycerin	50.0%

SUMMARY

1. In inhalation therapy with nebulized solutions, the choice of a nebulizer is not a matter of indifference. In fifty-nine samples representing fifteen brands of commercial nebulizers there was a 40-fold variation in the amount of solution delivered by one compression of the hand bulb. No one model was found best for all purposes.

2. Certain samples emitted droplets by hand bulb compression, and for this same reason certain ones could not be used with oxygen at 8 liters per minute or with compressed air at 40 pounds per square inch.

3. Individual models of commercial nebulizers are illustrated and discussed.

4. The formulas of certain commercial and noncommercial epinephrine solutions for inhalation therapy are given.

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ALLERGIC RHINITIS: COMPLETE DENTAL X-RAY EXAMINATION IN SEARCH FOR DENTAL FOCI OF INFECTION

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THE role of supersensitivity to microbial antigens in clinical allergy is one of the most controversial questions of this field.[1,3-6] Single clinical observations can but little contribute to the solution of this problem. However, many of us have been impressed by the favorable influence of the elimination of foci of chronic infection upon allergic conditions. This is illustrated by the following case history. It seems to be worth while reporting because it emphasizes the need for a thorough search for foci of infection, which in this particular case was located only after a complete dental x-ray examination.

CASE REPORT

The patient, a Second Lieutenant in the Chemical Warfare Service of the United States Army, was referred to the Allergy Clinic at Ft. Logan, Colorado, August 11, 1944, because of an alternating nasal blockage, mucoid rhinorrhea, and occasional sneezing.

There was no history of itching of the eyes or nose, and there were no eye complaints. These symptoms were constant and necessitated frequent visits to the Ear, Nose, and Throat Clinic. The symptoms began when the patient started work as a student in a chemical warfare service plant in Maryland in March, 1943. He stated that the weather was "cold" at the time, and his duties required his going on marches and bivouacs. From March, 1943, until October 1, 1943, the officer was transferred frequently and spent some time in Alabama, Virginia, and Miami, Florida. In October, 1943, he was transferred to Ft. Logan, Colorado. During all these moves about the country, his symptoms continued, except during the month of April, 1943, while in Alabama, where the symptoms were mild, and while in Miami, Florida, when, as a training officer working out of doors almost continuously, he was practically symptom-free. In October, 1943, after his transfer to Ft. Logan, the nasal obstruction and rhinorrhea became much more severe, and especially so starting in November, 1943. At Ft. Logan he continued his work as a Chemical Warfare Service officer. This brought him in contact with all Chemical Warfare Service materials. The patient was newly married. The patient also stated he kept a cat as a pet in his house. Inhalation of house dust in large quantities caused occasional sneezing but no real difficulty. His history revealed no relation to foods. It was noted that the patient was worse during the day and that the complaints did not keep the patient up at night. He also stated that he was definitely worse indoors. After nasal polypectomy in January and again in August, 1944, the symptoms were partially relieved for about one week each time.

Family History.—Negative for allergic diseases.

Past History.—

Medical: Irrelevant.

Surgical: Nasal polypectomy in January, 1944, and again in August, 1944. Tonsillectomy and adenoidectomy at the age of nine years.

Injuries: In 1938 he fell on his face, thereby breaking a tooth and lacerating his chin and lip. At the time he was dazed, but not unconscious.

Venereal Disease: Denied.
Social history: Married since April, 1943. He smoked a pipe occasionally.

Physical Examination.—He was a well-nourished and well-developed twenty-three-year-old white man who did not appear acutely or chronically ill. Head and eyes: slight conjunctival injection. Ears: normal external auditory canal; tympanic membranes normal. Nose: the left inferior turbinate was pale, and polyps were seen. Pharynx: essentially negative. The remainder of the physical examination, including neck, heart, lungs, abdomen, extremities and lymph glands, revealed no pathological findings.

Laboratory Data.—

1. Oral dental examination revealed the patient to be in Class IV, normal.
2. On October 28, 1944, x-ray of the sinuses showed changes of both maxillary sinuses suggestive of hypertrophic sinusitis. An x-ray of the sinuses taken May 4, 1944, revealed some clouding of the right maxillary antrum and slight clouding of the frontal sinuses. The other sinuses appeared clear.
3. Pathological report of nasal polyps removed in August, 1944: Gross—Specimen consists of two disc-shaped pieces of pearl white edematous tissue, 0.8 by 0.3 cm., and 0.66 by 0.2 cm. Microscopic—Numerous eosinophiles.
4. Dental consultation with full dental x-rays revealed a periapical abscess of the upper right lateral incisor.
5. Allergy tests: Intradermal tests—House dust gave a 1+ reaction to 100 PNU, 2+ to 1,000 PNU, and 3+ to 10,000 PNU. There were 2+ reactions to white potato, apple, and tobacco 1-10, lemon gave a 1+ reaction. Cat ep, dog ep, rabbit ep, feathers, cottonseed, flaxseed, kapok, silk, pyrethrum, fish glue, orris, human dander, egg white, milk, wheat, beef, chicken, pork, fish, cornmeal, lima bean, orange, mustard, green pea, banana, chocolate, peanuts, barley, rye, buckwheat, asparagus, beets, cabbage, carrot, celery, sweet corn, shrimp, grape, grapefruit, peach, and pineapple were all negative. The molds Alternaria, Aspergillus, Hormodendrum, Helminthosporium, Spondylocladium, Penicillium, and Fusarium, were essentially negative on testing to extracts of 1,000 PNU per c.c. with readings at twenty minutes, twenty-four hours, and forty-eight hours. The following pollens were tested in 100 PNU, 1,000 PNU, and 10,000 PNU strengths and were all found essentially negative: timothy, plantain, ragweed, ash, beech, birch, elm, hickory, oak, sycamore, carelessweed, lamb's-quarters, Russian thistle, redroot pigweed, sagebrush, and summer cypress. Patch tests to shaving cream (Burma Shave), face powder, activated charcoal, lipstick, cold cream, rouge, hand lotion (Jergens), talc and zinc hexachlorethane were all negative; readings were made after forty-eight hours with the patches in place and again in forty-eight hours after the patches were removed. Inhalation tests by having the patient inhale through his nose small amounts of the following substances gave no change in the subjective or objective nasal complaints: Jergens' lotion, face powder, Woodhue, talc (stored in the Chemical Warfare Warehouse), activated charcoal and soda lime, Burma Shave, lipstick, rouge, and zinc hexachlorethane.

Unfortunaetly, the blood picture in this case is not available, and no bacterial examination of the apical abscess was made.

Course.—On August 29, 1944, the abscessed tooth was removed and in about four days all nasal symptoms except for slight and occasional nasal blockage disappeared. He needed no nasal treatment from the latter part of August, 1944, until last seen in March, 1945. There was as yet no recurrence of symptoms. This was the first time since March, 1943, that this patient had had such marked and prolonged relief. This improvement occurred in spite of the fact that this patient continued at the same job.

DISCUSSION

It appears that this patient had an allergic rhinitis, as proved by the definitely pale nasal mucosa with watery rhinorrhea and by the pathological examination of the nasal polyp showing numerous eosinophiles on microscopic examination. He was found to have an abscessed tooth which remained unrecognized on routine oral dental examination and was only found after a full dental x-ray examination. Following removal of the abscessed tooth, remission occurred.

From a practical standpoint, this case shows that in the search for a focus of infection in the teeth, it is essential to have a complete x-ray examination of the teeth, with a careful interpretation, before one can be sure that such an infection does not exist.

The sequence of events is suggestive of a causal connection between the dental focus and the allergic condition of the nose. Different explanations of our experience—as, for instance, a nonspecific influence of the elimination of infective foci—cannot be excluded. It is well to realize that a single experience like the one reported here can be no more than a building stone for the establishment of evidence.

SUMMARY

1. A case of allergic rhinitis is reported in which removal of an abscessed tooth was followed by a remission.

2. The focus of infection in the tooth was found only on complete x-ray examination of the teeth.

3. It is suggested that complete dental x-ray examinations are useful in the search for foci of infection.

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Instead of crying, "Can we afford some new service?", we are now tending to realize that we cannot afford ill-health and the resulting loss of productive work. We are beginning to realize that expenditure on preventive services and on health research pays an enormous dividend.—Sir Andrew Davidson, *British Medical Journal*, Feb. 7, 1948.

MULTIPLE SCLEROSIS—TREATMENT WITH HISTAMINE AND d-TUBOCURARINE

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MULTIPLE sclerosis is a disease of the central nervous system characterized by exacerbations and remissions. It has long been recognized that the early symptoms of multiple sclerosis are often mistaken for hysteria. There appear to be several reasons for this error. The first complaints often seem bizarre, and only few objective abnormal findings can be demonstrated on careful examination. The symptoms frequently disappear spontaneously. Thus it comes about that individuals who have a number of attacks of transient numbness or paralysis, later show definite signs of organic disease of the nervous system. Approximately one patient in twelve with the disease may be expected to require institutional psychiatric help at some time.[18] In 1836 or 1837 Sir Robert Carswell[16] described a pathological specimen of the pons and cord spotted with grey areas of atrophy. About thirty years later Charcot gave a review of the literature and named the disease.

There are multiple patches of sclerosis scattered diffusely throughout both the grey and the white matter of the cerebrospinal axis.[3] These are areas of glial overgrowth in which the nerve fibres are usually preserved, at least to the extent that the axis-cylinders pass through but are deprived of their myelin sheaths.[19] Careful studies of the degree of destruction within the plaques have given conflicting results. Putman,[23] on the one hand, states that in a little more than 50 per cent of the plaques there is complete or almost complete loss of nerve fibers; Greenfield and King,[9] on the other hand, report that in less than 10 per cent is there severe destruction, and that in the remaining, little or no diminution in the number of axis-cylinders is found. This divergence is probably to be explained by the difference in technique employed. It is this persistence of conducting elements that accounts for the absence of tract degenerations in multiple sclerosis.

The three types of the disease are acute, remittent and the chronic progressive. The remittent may become chronic progressive. Prognosis depends on the type. It is very poor for the acute rapidly progressive, and good for the other types. A hopeless prognosis should not be made.[27] As Von Hoesslin[33] pointed out, the prognosis in cases of multiple sclerosis may by no means be as hopeless as many textbooks would lead one to believe. Substantial remissions, so complete that the patients considered themselves practically well, occurred in 17 per cent of his cases. About 70 per cent of cases appear between the ages of twenty and forty

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years. Less than 2 per cent occur before the age of ten, and 4 per cent after the age of fifty.[2]

Scheinber[26] expressed the view that the acute and the chronic forms of multiple sclerosis are varieties of the same morbid entity. The structural differences in the lesions are explained by the difference in intensity and duration of the same morbid process. There are many theories as to the cause of the disease, among them being that multiple sclerosis is the result of allergies. In 1938 Kennedy[17] and Pardee[22] among others called attention to allergic reactions in the central nervous system, Kennedy pointing out the possibility that multiple sclerosis is the result of allergy. Of this Carter[5] says: "The short and transitory remissions and exacerbations of symptoms can be readily thought of as being due to transitory allergic tissue edema which interrupts function of the central nervous system temporarily, and that permanent loss of function comes only after prolonged or repeated episodes of tissue hypersensitivity."

Earlier, A. Ferraro[7] said: "The pathologic syndrome of all demyelinating diseases appears plausible as the expression of an allergic reaction or nerve tissue. With this conception of a common cause applied to many seemingly unrelated clinical entities, we have used histamine as a therapeutic agent with marked success in many subjects."

Shortly thereafter, Horton,[10,14] Sollman,[29] MacLean and Craig,[14] Shelden,[28] Rainey,[24] Thomas and Butler,[32] Brown,[13] Roth,[13,25] Rynearson,[25] Alexander and Elliott,[1] Christian[6] and many others reported the successful treatment of many neuroallergies with histamine. In 1943 Horton and his co-workers Wagener, Woltman and Woltman[15] reported the treatment of 102 cases of multiple sclerosis with the daily intravenous administration of 2.75 mg. of histamine diphosphate in 250 c.c. of isotonic solution of sodium chloride. This report indicated varying degrees of improvement in over 50 per cent of the cases.

Following this report, we began the use of histamine diphosphate both intravenously and subcutaneously in different neuroallergies including multiple sclerosis. For more than two years we have been using histamine diphosphate in the treatment of multiple sclerosis, first using prostigmine combined with histamine, and later d-Tubocurarine, with muscle re-education and allergy management. During this time, we have treated 124 cases, seventy-five females and forty-nine males. The reason for this divergency by sexes is probably economic. The wife with multiple sclerosis is able to come and be treated. On the other hand, should the husband be the victim of the disease, it is difficult financially for him to leave home to take treatment. Practically all of our cases have been of the chronic progressive type; only six could be classified as acute. Age is a major factor in the disease, the vast majority of the cases having their first attack between twenty and forty. The average age of onset in our series for females was 29.16 years, and for males, 30.41 years. The oldest at onset was forty-nine for males and forty-nine for

females. The youngest onset in our series was fifteen for females and twenty for males. The average duration of the disease for females was 9.48 years, and for males, 11.34 years.

All of our patients came to us with a definite diagnosis of multiple sclerosis made at a recognized neurological clinic or by a reputable neurologist. Those that came with the diagnosis made under other circumstances, were referred to competent neurologists for a thorough neurological examination and report. We were not responsible for the diagnosis of multiple sclerosis in any case, although we concurred in the diagnosis of multiple sclerosis before starting treatment.

SYMPTOMS

The most marked symptom that was noted in our cases was that of weakness and exhaustion on effort. Practically all complained of this condition at one time or another. Nystagmus was present in most of the cases, with diminished abdominal reflexes, while the deeper reflexes of the lower extremities were markedly exaggerated in most patients. Bladder symptoms, speech hesitancy and gait disturbances were present in about half of the patients. Tremors and emotional instability with personality changes were also present in about one-half of our patients. Visual impairment with a history of diplopia and optic neuritis occurred in a large percentage of the cases. About half of our patients were bedfast or confined to wheel chairs. In some, tremors and spasticities were so violent that it was necessary to use restraining sheets at first. These latter cases responded to treatment rapidly and very satisfactorily. About 20 per cent suffered from pain in varying degrees, which also responded quickly in the majority of our cases. Sixty-three suffered from quadriplegia, paraplegia or hemiplegia.

In multiple sclerosis, spasticity is one of the principle disabling factors; therefore, if the spastic condition can be relieved and the tremors controlled, the patient may become a useful worker again. Nearly all of the cases of multiple sclerosis were of the chronic progressive type, most of them being very spastic. To help control this spastic condition and the intention tremors, we were of the opinion that curare would be the best drug. The problem was to find a preparation that could be given in sufficiently large doses to control spasticity and tremors and still be safe. Bernard[4] had shown that curare causes an elective release of rigidity in spastic muscles while the normal musculature was unaltered. This release may be enough to convert a hand which is entirely useless into one in which active co-ordinate motion can be accomplished. While curare will not convert a paralyzed muscle into an active one, the release of the rigidity may allow a muscle not completely paralyzed to begin functioning actively. Curare produces its effect by an elective affinity for the hyperinnervated myoneural junction. It is also an autonomic

blocking agent active mainly on skeletal muscles and to a lesser degree on autonomic ganglia.[8] It does not paralyze smooth muscle.[20]

D-TUBOCURARINE

d-Tubocurarine is the most effective and stable of the various curare alkaloids. We found that d-Tubocurarine in the aqueous solution was too fleeting in its action to be of any value. Prolonged action was necessary to permit any activity on the part of the patient. A suspension of d-Tubocurarine made according to the formula of Schlesinger,[27] and containing 30 mg. per c.c. of d-Tubocurarine in a base composed of 4.8 per cent white beeswax in peanut oil,* was used. This was given deep into the muscle in doses that varied from 7.5 mg. every fourth day up to as much as 120 mg. daily. There was a wide range in dosage among patients, the effects in some lasting as long as ninety-six hours, in others only twelve to sixteen hours.

The action of the d-Tubocurarine in oil and wax was startlingly good. This preparation gave prolonged action with constant effects. It gave an immediate feeling of relaxation and comfort to the tense, spastic patients. The first dose often gave them the first comfortable night's sleep they had had in years. Incontinence and frequency of urination were improved or controlled in a very short time in every case. Constipation, the "bugaboo" of multiple sclerosis, was relieved in most patients within a few weeks. Tremors were markedly reduced in all cases. Voluntary movements previously blocked by spastic rigidity were made possible and patients were able to move hands, arms, legs and other parts of their body in varying degrees approaching normal. These limbs had previously been paralyzed or uncontrollable through spasticity and tremors.

Following the prolonged use of d-Tubocurarine, there appeared an accumulative action with the development of an increased sensitivity to its action. Smaller doses could then be given at increased intervals with constant effect. Some patients were able to go for a month to six weeks without a noticeable return of tremors, muscle rigidity or spasticity. Because of this, patients were able to take vacations from treatment at varying intervals with a good effect on their morale.

We have given over 20,000 doses of d-Tubocurarine in the last eight months without a single undesirable reaction. Neither has there been any tendency to habituation in any case. As a matter of fact, the patients all seem to want to decrease their dose as rapidly as possible. This is because the accumulative effect is prone to produce uncomfortable dizziness, slight visual symptoms or other side effects, unless the amount of the drug given is gradually decreased. Also, at certain times after the drug has been administered over a period, there will develop a "stiffness" or lack of power in all four limbs and lower jaw. This condition is relieved by withdrawal of the drug for a week or ten days.

*Supplied through the courtesy of the Abbott Research Laboratories.

TABLE I. FORTY CHRONIC PROGRESSIVE MULTIPLE SCLEROSIS CASES
Treated at St. Joseph's Hospital, Tacoma, Wash., Nov. 15, 1947 to Feb. 15, 1948

Case No. Age Occupation	Surgery Trauma Accidents	Allergies	Attacks Type	Previous Treatment Results	Symptoms on Admission	Histamine Diphosphate	d-Tubo-Curarine In Oil and Wax	Present Condition
1. Mr. M. W. 60. Yeastmaker.	None.	Rhinitis. Foods. Molds.	1925 Ch. Prog.	None.	Urinary Incontinence. Spastic Paraplegia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Urinary incontinence stopped. Paraplegia improved.
2. Mrs. L. A. 49. H. W.	None.	Hives. Foods.	1933 Ch. Prog.	Small amount of Histamine once weekly for six weeks.	Spastic Paraplegia. Paresthesia. Dyspharthria. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	22.5 mg. 3 times weekly.	Spastic Paraplegia improved. Walking. Dyspharthria improved. Pollakiuria improved. Amblyopia improved.
3. Miss G. S. 43. Telephone Operator.	Fractured right leg 1945. Appendectomy. Double mastoid	Rhinitis. Eczema as child. Food. Epidermals.	1941 Cr. Prog.	Fever therapy Improved.	Amblyoia. Hippus. Spastic Paresis all 4 limbs. Pollakiuria. Cane case.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Amblyopia, Hippus and Pollakiuria all marked improvement. Spastic paresis entirely controlled. Does not use cane at all.
4. Mrs. M. P. 46. H.W.	None	Many foods.	1932 Ch. Prog.	None.	Spastic Quadriplegia, Dysphasia Oscillopsia. Complete incontinence. Retention catheter. Bed-fast 13 years.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. daily.	Homesick. Left hospital after six weeks. No improvement.
5. Miss G. M. 25. Telephone Operator.	Pelvic lap. 1946. Stung by "yellow jacket" 1938. 2 weeks later 1st symptoms.	Rhinitis Neuroderma.	1939, 1941 Remittent. 1947 Ch. Prog.	Histamine I.V. daily 3 mos. Prostigmine 14 injections daily. Worse.	Dysphagia. Dysphasia. Spastic Quadreplegia. Oscillopsia. Left external Strabismus. Pollakiuria. Left amaurosis. Bed-fast 6 mos.	2.75 mg. daily for 10 days, then 3 times weekly.	60 mg. daily.	Dysphagia improved. Dysphasia slight improvement. Spastic Quadriplegia marked improvement. Strabismus improved. Pollakiuria entirely relieved. Left amaurosis improved. In wheel chair.
6. Mr. K. B. 36. Sailor.	Appendectomy 1936.	Colds. Foods.	1938, 1939 Remittent. 1940 Ch. Prog.	None.	Dysasthria. Dysphagia. Paresthesia. Spastic Quadriplegia. Opthalmoplegia. Diplopia. Pollakiuria. Amblyopia. Partially bed-fast.	2.75 mg. daily for 10 days, then 3 times weekly.	120 mg. daily.	All symptoms improved.
7. Mrs. L. F. 28. Bakery clerk.	None.	Foods.	Emotional family upset June '40. Within 2 weeks left leg paralyzed. 1940, 1941 Remittent. 1941 Ch. Prog.	None.	Dysphagia. Dysphasia. Decubitus. Spastic Quadriplegia. Hippus. Bed-fast four years.	2.75 mg. daily for 10 days, then 3 times weekly.	60 mg. daily.	Some improvement of all symptoms.
8. Mrs. F. C. 34. H. W.	None.	Foods. Pollens Epidermals.	1937, 1938 Remittent. 1939 Ch. Prog.	None.	Dysarthria. Sastic Quadriplegia. Oscillopsia. Hippus. Bilateral External Strabismus. Euphoria. Highly emotional. Wheel chair. Urinary Incontinence.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Slight improvement some symptoms.

TABLE I. (Continued)

9. Mrs. L. C. 42. H. W.	None.	Foods. Epidermals.	1930 Ch. Prog.	None.	Paraplegia. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Pollakiuria and Amblyopia improved. Paraplegia unimproved.
10. Mr. L. B. 48. Barber.	Appendectomy 1922.	Foods. Human hair.	1938 Ch. Prog.	Prostigmine. No results.	Spastic paraplegia. Cane case 3 years.	2.75 mg. daily after 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Walks without cane and did so after first injection of d-Tubocurarine.
11. Mrs. M. B. 28. H. W.	None.	Eczema all life. Molds. Pollens Foods.	1938, 1940 Remittent. 1941 Ch. Prog.	Histamine. Improved.	Euphoria. Dysarthria. Marked spastic condition, all 4 limbs. Paraplegia. Oscillopsia. Pollarkiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Marked improvement of all symptoms.
12. Mrs. K. E. 31. H. W.	Cesarean section Cervical sympathectomy. Submucous resections.	Rhinitis. Hay fever. Eczema. Foods.	1941. Ch. Prog.	Sympathectomy.	Very spastic. Paresis left arm and left leg. Oscillopsia. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	In Oil and wax. 30 mg. daily.	Spastic condition so improved after 30 days treatment that patient was able to take a 3,000 mile automobile trip. Husband giving her 30 mg. of d-Tubocurarine daily.
13. Mrs. L. E. 32. H. W.	Thyroidectomy 1936. Appendectomy 1945. T. & A. 1945.	Foods.	1945 Ch. Prog.	Histamine. 30 doses. Improved condition.	Dysarthria. Urinary incontinence. Oscillopsia. Amblyopia. Diplopia. Very spastic Paraplegia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. daily.	All symptoms improved. Incontinence relieved after first dose of d-Tubocurarine. Walks with some help.
14. Mr. F. G. 40. Steam Engineer.	None.	Foods.	1942 Ch. Prog.	None.	Urinary incontinence. Paresthesia and Spastic paresis of both lower extremities.	Continuous as his time will permit up to 88 mg. in 8,000 cc normal saline during 48 hours.	30 mg. 3 times weekly.	Incontinence stopped after first dose of d-Tubocurarine. All other symptoms improved.
15. Mr. E. F. 33. Milk dealer.	Fractured ankle 1940.	Foods. Molds.	1941, 1943 Remittent. 1943 Ch. Prog.	1943 had 12 fever "shots." Improved. '47 one month Dicumeral treatment. No improvement.	Dysarthria. Oscillopsia. Diplopia. Paraplegia. Pollakiuria. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Pollakiuria marked improvement. All symptoms improved.
16. Mr. J. W. 38. Office Worker.	None, and none recommended.	Foods. Hay fever. Asthma.	Ch. Prog. 1941	None.	Spastic Paraplegia. Paresthesia. Pollakiuria. Wheel chair.	Continuous as indicated up to 44 mg. in 4,000 cc normal saline during 48 hours.	30 mg. 3 times weekly.	Pollakiuria relieved after first injection of d-Tubocurarine. Other symptoms improved.
17. Mrs. E. S. 43. Reg. Nurse.	None.	Foods. Molds. Brother and sister, asthma and hay fever.	1940, 1944 Remittent. 1944 Ch. Prog.	25 Histamine I. V. injections. No improvement.	Spastic Paraplegia. Oscillopsia. Pollakiuria. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Pollakiuria relieved entirely all other symptoms markedly improved. Walking with help now.

TABLE I. (Continued)

Case No. Age Occupation	Surgery Trauma Accidents	Allergies	Attacks Type	Previous Treatment Results	Symptoms on Admission	Histamine Diphosphate	d-Tubo-Curarine In Oil and Wax	Present Condition
18. Mrs. D. H. 35. Stenographer.	None.	Hives. Eczema.	1940, 1944 Remittent. 1944 Ch. Prog.	1944, 40 injections Histamine. Improved.	Dysarthria. Spastic Paresis both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
19. Mr. E. A. 32. Truck Driver.	Appendectomy 1943.	Rhinitis.	1945, 1947 Remittent. 1947 Ch. Prog.	None.	Diplopia. Amblyopia. Pollakiuria. Spastic Paresis, both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms slightly improved.
20. Mr. G K. 54. Meat Cutter.	Left inguinal hernia 1943. Right inguinal hernia and appendectomy 1947.	Eczema. Rhinitis.	1943 Ch. Prog. immediately after operation.	Histamine 30 I. V. 2.75 mg. daily. Improved.	Dysarthria. Paresthesia. Hippus. Pollakiuria. Spastic paresis both lower extremities. Amaurosis.	2.75 mg. daily.	30 mg. daily.	All symptoms markedly improved.
21. Mr. R.A.W. 47. Farmer.	None.	Food.	1935 Ch. Prog.	None.	Diplopia. Amaurosis. Urinary incontinence. Dysarthria. Spastic paresis, both lower extremities.	2.75 mg. daily.	30 mg. daily.	Incontinence stopped. Other symptoms improved.
22. Mrs. G. L. 41. H. W.	Adhesion of dorsal spinal cord loosened 1939.	Hay Fever. Asthma. Eczema.	1936 Ch. Prog.	None.	Spastic paraplegia. Dysarthria Urinary incontinence. Amblyopia. Oscillopsia. Wheel chair.	2.75 mg. daily.	30 mg. daily.	Urinary incontinence stopped. All other symptoms improved.
23. Mr. N. S. 52. Hydroelectric Worker.	Sympathectomy 1935.	Foods. Molds.	1928, 1930 Remittent. 1932 Ch. Prog.	Sympathectomy.	Left spastic hemiplegia. Pollakiuria.	2.75 mg. daily.	15 mg. daily.	Improved.
24. Mrs. M. W. 27. H. W.	Tubal pregnancy operation April 15, 1946. One week later M. S. developed.	Foods. Molds.	Ch. Prog. 1946, immediately after operation.	None.	Dysarthria. Spastic paresis both lower extremities. Pollakiuria.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
25. Mr. G. F. 35. Salesman.	Fractured right ankle 1938.	None.	1935 Ch. Prog.	Prostigmine. 6 mos. No results.	Dysphagia. Spastic Quadriplegia. Dysphasia. Decubitis. Urinary incontinence. Amaurosis. Bed-fast.	5.50 mg. daily.	60 mg. daily.	Up in wheel chair. A few steps. All symptoms markedly improved.
26. Mr. R. E. 42. Druggist.	None.	None.	1941 Ch. Prog.	None.	Incontinency of urine. Hippus. Dysarthria. Spastic paresis, both lower extremities.	2.75 mg. daily for 10 days, than 3 times weekly.	30 mg. 3 times weekly.	Incontinence stopped. All other symptoms markedly improved.
27. Mr. A. Z. 45. Sawmill worker.	Appendectomy 1918. Head injury 1938.	None.	1938 Ch. Prog. immediately following head injury.	None.	Dysphagia. Hippus. Dysphasia. Spastic paraplegia. Pollakiuria. Amaurosis. Euphoria. Bed-fast.	5.50 mg. daily.	30 mg. daily.	Up in wheel chair. Walks a few steps. All symptoms improved.

TABLE I. (Continued)

28. Mrs. H. A. 36. Bookkeeper.	Caesarian section 1942. Appendectomy 1937.	None.	1938, 1941 Remittent. 1941 Ch. Prog.	Prostigmine for 1 yr. No improvement.	Dysarthria. Spastic paraplegia. Oscillopsia. Diplopia. Pollakiuria.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Generally improved.
29. Mr. O. R. 33. Automobile Mechanic.	Industrial accident Aug. 1937. Right ankle injured.	None.	Aug. 1937 Ch. Prog. since accident.	Quinine. 3 mos. No result.	Spastic paraplegia. Pollakiuria. Parethesia. Amblyopia. Wheel chair.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Walks a few steps. All symptoms improved.
30. Mr. W.M.B. 28. Salesman	None.	Molds.	1943 Ch. Prog.	None.	Spastic paresis both lower extremities. Paresthesia. Pollakiuria.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
31. Mrs. A. R. 52. H. W.	Pelvic lap. 1942. Tonsilectomy 1942.	Hay fever.	1945, 1946 Remittent. 1946 Ch. Prog.	None.	Spastic left hemiplegia. Dysarthria. Paresthesia. Pollakiuria. Bed-fast.	5.50 mg. daily.	60 mg. daily.	In wheel chair. Walks a few steps. Marked general improvement.
32. Mr. I. M. P. 54. General Laborer.	Sinus 1934. Prostatectomy 1943.	Rhinitis.	1931 Ch. Prog.	None.	Spastic paresis both lower extremities. Oscillopsia. Pollakiuria. Dysarthsia. Amblyopia.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
33. Mrs. E. R. 42. School Teacher.	None.	Eczema since 3 months old.	1946, 1947 Remittent. 1947 Ch. Prog.	None.	Dysarthria. Oscillopsia. Pollakiuria. Spastic paresis all four limbs. Euphoria.	5.50 mg. daily.	30 mg. daily.	All symptoms improved.
34. Mrs. D. G. 43. H. W.	None.	Pollens.	1946 Ch. Prog.	None.	Pollakiuria. Paresthesia. Dysarthria.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	All symptoms improved.
35. Mrs. V. K. 25. H. W.	None.	Foods. Epidermals.	1939, 1947 Remittent. 1947 Ch. Prog.	None.	Paresthesia. Spastic Paresis all four limbs.	2.75 mg. daily for 10 days, then 3 times weekly.	15 mg. 3 times weekly.	Improved.
36. Mr. R.B.D. 43. Sheet Metal Worker.	None.	Asthma.	1944 Ch. Prog.	None.	Paresthesia. Pollakiuria. Amblyopia. Spastic Paresis both lower extremities.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Pollakiuria improved.
37. Mr. L.H.H. 48. Grocer.	Appendectomy 1928. Double inguinal Herniotomy 1917.	Asthma 1926 to 1936.	1936 Ch. Prog.	40 injections I. V. Histamine. No improvement.	Spastic paraplegia. Pollakiuria. Amblyopia. Dysarthria.	5.50 mg. daily.	30 mg. daily.	All symptoms improved.
38. Miss L. W. 35. Stenographer	Spinal tumor fibroids Sept. 1943. Pelvic lap. Oct. 1943. Bladder operation Jan. 1945.	Pollens. Epidermals.	1943 Ch. Prog.	None.	Amblyopia. Dysarthria. Paresthesia. Urinary incontinence.	2.75 to 11 mg. daily.	15 mg. daily.	Generally improved.

TABLE I. (Concluded)

Case No. Age Occupation	Surgery Trauma Accidents	Allergies	Attacks Type	Previous Treatment Results	Symptoms on Admission	Histamine Diphosphate	d-Tubo-Curarine In Oil and Wax	Present Condition
39. Mrs. W. S. 47. H.W.	Cervical dorsal sympathectomy for multiple sclerosis, 1941.	Rhinitis.	1926, 1937, 1938 Remittent. 1939 Ch. Prog.	Sympathectomy 1941.	Spastic paraplegia. Paresthesia. Pollakiuria. Amblyopia.	2.75 mg. daily for 10 days, then 3 times weekly.	30 mg. 3 times weekly.	Unchanged.
40. Miss F.L.K. 58. School Teacher.	Left mastoid operation 1930.	Eczema until age 15. Hay fever.	1926, 1929 Remittent. 1930 Ch. Prog.	Quinine 2 weeks. Fowlers solution 2 weeks. No results. Histamine 25 injections, improved.	Spastic paresis both lower extremities. Pollakiuria. Dysarthria.	2.75 mg. daily.	30 mg. daily.	Generally improved.

AGE SUMMARY

	No.	Oldest Now	Oldest At Onset	Youngest Now	Youngest At Onset	Longest Duration	Shortest Duration	Average Age now	Average Age Onset	Average Duration
Female	22	58	49	25	15	22	2	38.3	27.5	10.8
Male	18	60	49	28	22	23	3	42.7	32.1	10.6

PHYSICAL THERAPY

In conjunction with d-Tubocurarine, we use physical therapy, depending upon muscle re-education and hot packs. Both of these measures are used in the same manner as in the treatment of the residuals of poliomyelitis. The d-Tubocurarine so relieves the spastic conditions that when voluntary impulses get by the myoneural junction, muscle re-education is needed for the proper control of the affected limb. The hot poliomyelitis packs are of marked value in helping to break down contractures. We are able to get rigid, badly contracted limbs straightened out with the assistance of these hot packs, where, as in some cases, it is difficult to do so with d-Tubocurarine alone. Massage, either heavy or light, is not used by us, as it seems to aggravate all spastic conditions. Mild exercises are encouraged. However, we insist on all of the multiple sclerosis patients taking as much rest as possible; and those that are working are told to curtail all outside activities that are tiring.

ALLERGY MANAGEMENT

All patients are tested for their sensitivity to foods, epidermals, molds, fungi, pollens and miscellaneous allergens. The proper diets from an allergy standpoint are prescribed, and they are all given an allergenic extract. The extracts are made using histamine diphosphate in normal saline, .275 mg. per c.c. as a base. This is injected subcutaneously in increasing doses in the same manner that histamine is given. Following the release from active treatment, the extract can be self-administered as a prophylaxis against exacerbations of multiple sclerosis.

HISTAMINE

Our entire study was based on the theory that allergy is the etiological cause of multiple sclerosis. Therefore, our patients are given histamine diphosphate intravenously to the point of tolerance. Some received 2.75 mg. histamine diphosphate in 250 c.c. normal saline daily and others a continuous infusion[30] of 11 mg. histamine diphosphate in 1,000 c.c. of normal saline at a rate of 30 drops per minute, every six hours, alternating with 11 mg. histamine diphosphate in 1,000 c.c. of 5 per cent glucose solution. This continuous infusion would be given for periods of twenty-four, and in some cases forty-eight, hours. Our best results were in the cases that were able to take the larger amounts. In the cases where histamine had been a failure before coming to us, we believe that too little had been given for too short a time. A number of these patients when given larger amounts responded very satisfactorily. In the cases where only small doses of histamine diphosphate were tolerated, we gave glucophylline (theophylline[34]) with the idea of prolonging vasodilatation. Using histamine, we accomplished two purposes: first, the hyposensitization of the patient to the histamine reactions of allergy; and, second,

the benefit derived from histamine as a vasodilator, being the most effective vasodilator known on the tissues of the central nervous system.

In our series we have administered histamine diphosphate intravenously over 10,000 times and have had no noticeable reactions. A number of our patients have come to us with histories of reactions when histamine had been given to them previously. However, they did not have these reactions when given histamine in our clinic. We are of the opinion there are two reasons for this. When intravenous histamine is given too rapidly, reactions are bound to occur. There is also the pyrogenic factor as in all intravenous medication. This may explain some of the reactions as being the result of the improper sterilization of glassware or rubber tubing. We never administer histamine diphosphate intravenously any faster than 2.75 mg. histamine diphosphate in 250 c.c. of normal saline, or in 250 c.c. of a 5 per cent glucose solution, in less than one hour and thirty minutes.

CLIMATE

We noticed that all of our spastic patients exhibit more rigidity on cold days, and that all were better when the weather was warmer. A number of writers have spoken of this before.[31] Another symptom that cold weather seemed to produce, and which appeared to have a market effect on the disease, was a typical "cold in the head." A majority of multiple sclerosis patients mentioned this. Patients would have several of these "colds" each year, and following each attack, the symptoms of multiple sclerosis would be worse. "Colds" appeared to be much more prevalent during the winter months when the days were short. Attacks of sinusitis and rhinitis undoubtedly play a major role in some way in bringing on exacerbations and intensifying symptoms. This undoubtedly explains in a way why multiple sclerosis is looked upon as a disease of the colder climates, and why a great many of these cases improve when they go to a warm dry climate. In all the inquiries to us regarding treatment, there were practically none from the southern half of the United States. The majority of inquiries outside of the states of Washington, Oregon and Idaho came from Montana, Minnesota, Michigan, the Dakotas and Canada. In our entire series, we had only two patients from California; one from near Oakland and one from near Los Angeles. Several of our patients, following treatment with us, went to Southern California and Arizona and continued to improve while spending the winter months in the South.

SUMMARY AND COMMENTS

Summarizing our 124 cases, we find that nearly all had some form of allergic sensitivity. Those with multiple food sensitivities apparently were, as a general rule, our most severe cases; they were more spastic than those with other allergies, and their tremors were much more difficult to

control. Sixty-one of our patients reacted strongly to scratch testing with food allergens. However, we did not depend upon the scratch test wholly, and in the severe cases we used elimination diets and careful observation of the effects of various foods from a clinical standpoint. In Case No. 3, eggs would produce nystagmus immediately. Cases No. 22 and No. 55 would have aggravation of symptoms following the drinking of tea, and Case No. 20 would suffer an aggravation of symptoms immediately following the eating of pork. Case No. 47 became worse symptomatically, and, in studying her diet, we found that she had been eating a large quantity of rhubarb, which was seasonal. The patient had not been tested for her allergic sensitivity to rhubarb, therefore we eliminated it from her diet at once and her symptoms began to improve. At the end of two weeks, her condition had returned to what it was symptomatically prior to the eating of the rhubarb.

Twenty-six had allergic rhinitis. Twenty-two were sensitive to various molds. Twenty-four had eczema or had suffered from eczema previously. Seventeen were sensitive to epidermals. Twelve were sensitive to pollens. Eighteen gave a history of hay fever. Sixteen gave histories of asthma, and ten gave histories of urticaria. Two of our patients with multiple sclerosis grew worse while being treated. Of these, Case No. 33 suffered from a vicious exfoliative dermatitis which came on at the same time the multiple sclerosis symptoms first developed; she was very sensitive to house dust and cotton. Histamine appeared to be of very little value in her case, either for the dermatitis or the multiple sclerosis. The second case which grew worse was Case No. 98. This patient had many blebs on his body at the time his symptoms of multiple sclerosis grew worse, and neither were improved by histamine. Both of these patients suffered from hematuria with a mixed infection pyelitis. Case No. 1 was sensitive to many molds; he had been a yeast maker during the onset of his multiple sclerosis. Case No. 10, a barber, whose wife now operates a beauty college, reacted to human hair. Case No. 46, who had formerly been a printer, reacted violently when tested for newsprint sensitivity. No. 52 was very sensitive to lacquers; before the onset of his multiple sclerosis he had been an automobile painter, using a spray gun. Pregnancy apparently may play an important part, as twenty-four of the sixty-two married women treated by us developed the symptoms of multiple sclerosis during pregnancy or shortly thereafter. Four of these patients had cesarean section. Of the forty-eight male patients, eleven gave histories of major trauma immediately or shortly before their symptoms of multiple sclerosis first appeared; and ten of the forty-eight men developed their first symptoms of multiple sclerosis while serving in the armed forces during World War II.

Tabulating the results of our treatments up to date, we find the following:

Objectively symptom free	13
Marked improvement objectively	20
Improved objectively	38
Slightly improved objectively	33
Improved subjectively	8
No improvement subjectively or objectively	10
Worse than at the beginning of treatment	2
Total	124

Included in the above are the six acute cases, of which four are now objectively symptom-free, one markedly improved objectively, and one worse.

In some of the cases there was no improvement noted until about three months' time had elapsed, this improvement becoming more marked usually after about six months' treatment. However, in a great many of the milder cases, improvement began after a shorter duration of treatment. We are of the opinion that regardless of how soon improvement is noted, intravenous histamine should be continued regularly for at least one year, and much longer in most of the chronic progressive type of cases.

CONCLUSIONS

The study of our 124 patients has resulted in the following conclusions:

1. Multiple sclerosis is much more prevalent than commonly supposed.
2. Allergy management is apparently indicated in multiple sclerosis to get the maximum degree of improvement.
3. Early treatment yields better results and a greater possibility of bringing about a remission.
4. Histamine diphosphate given intravenously and subcutaneously is of great value, but must be given regularly and over a long period of time.
5. d-Tubocurarine, in oil and wax, controls spasticity or brings about improvement where tremors and urinary incontinence exist. Improvement or control took place quickly in over 80 per cent of our cases.
6. Muscle re-education with physical therapy increases the value of d-Tubocurarine.
7. Because of the time necessary for treatment and the expense involved, available financial aid is needed in any attempt to solve the problem of multiple sclerosis. Local organizations with affiliations, such as the National Infantile Paralysis Foundation, should be set up. Due to the crippling nature of the disease, the average patient cannot carry on financially for the time necessary as a private patient. Education and information, regarding the fact that the sufferers of this disease are not entirely hopeless, should immediately lead to a movement in the direction of adequate care and study of this crippling disease.
8. We do not claim to have cured a single case, although remissions have occurred following treatment, and a large majority of our cases have improved objectively. Practically all of our patients feel they have something to look forward to in the way of treatment, with hopes

for the future. This helps their morale and they are at least subjectively better. If, by treatment, we can make ambulatory or wheel-chair cases out of the bedfast ones, get some from their wheel-chairs onto canes and get others to discard their canes, much will have been accomplished.

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(Continued on Page 578)

A CHEMICAL CONCEPT OF IMMUNITY

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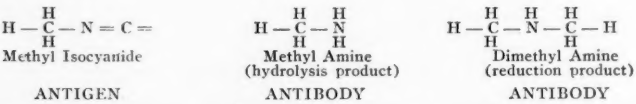
IMMUNITY continues to be so much a play with mere words that any attempt at chemical explanation should be welcomed. Few such have been made. Arrhenius and Madsen[1] showed that the union between a toxin and its antitoxin (diphtheria, tetanus) was like the neutralization of a weak acid by a weak alkali; and Bordet[2] declared it to be like a union between a dye and a fiber, at the latter's surface. Linus Pauling[5] has proposed that what is the (unknown) chemical termed a toxin is rendered inert through intramolecular rearrangement.

My own consideration began in the attempt to give chemical definition to what E. C. Rosenow had discovered as the toxic *antigen* of various streptococci and the *antibody* prepared therefrom. The latter was accomplished by subjecting streptococci and streptococcal antigen in sodium chloride solution, in an autoclave, to prolonged heating. Addition of hydrogen peroxide shortened the time required. Rosenow found the antigen and toxic factors in streptococcal suspensions to decrease and substances resembling antibody to increase under such treatment. The assumption is that the processing converts the antigen into antibody[6,7].

An immunological reaction consists in a newly formed antibody combining with its antigen to yield the immune body. This not only detoxifies the antigen but leads to the formation of further substance able to react with the antigen. The overplus represents the immunological reserve.

A type of organic reaction which suits this pattern is represented by what happens to an isocyanide (also called an isonitrile) when, through hydrolysis or reduction, it is converted to an amine. The former represents the toxin or antigen; the latter, the antitoxin or antibody. Simple illustration of the construction of such chemical bodies appears in the following formulas:



ANTIGEN ANTIBODY ANTIBODY

The immunological reaction consists of the union of antigen with antibody to form an amidine. In the illustration used, this transformation takes place in three steps as shown on the opposite page.

As indicated, one molecule of antibody is thus capable of neutralizing three molecules of antigen.* Since immune body production would not, in

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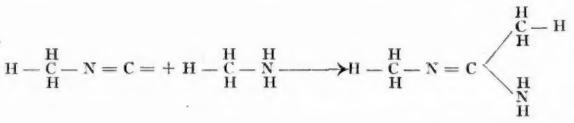
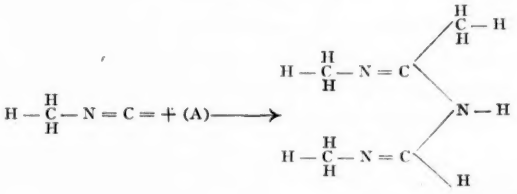
*The structural formulas of the amidines are often written in isomeric forms to those given above. They possess considerable bacteriostatic power.[3,4,5]

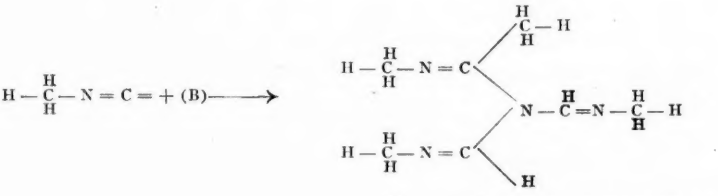
chemical terms, proceed beyond the first step in a disease attack, it follows that the intoxicated individual would have left over a reserve of immunity, potent in overcoming the arrival of more toxin. This explains why, because of immediate and large antibody production, the highly intoxicated organism inclines to recover more suddenly than one less poisoned, even though the continuing state of intoxication warrants the anticipation of his getting worse. Thus, the more seriously ill person is better off, in a certain sense, than one less stricken; his antibody production is greater.



Immune body (monomolecular union)
Amidine (A)

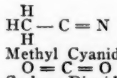


Immune body (dimolecular union)
Amidine (B)

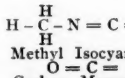


Immune body (trimolecular union)
Amidine (C)

The isocyanides should not be confused with their relatively harmless isomers, the cyanides. (The two forms exist in many cases in equilibrium with each other). Methyl cyanide, for example, is a relatively harmless substance, but not methyl isocyanide. The latter compound (here suggested as the chemical equivalent of antigen) may be compared to carbon monoxide; the former to carbon dioxide.



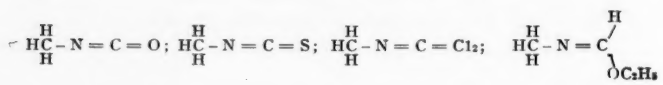
Methyl Cyanide
$O=C=O$
Carbon Dioxide



Methyl Isocyanide
$O=C=$
Carbon Monoxide

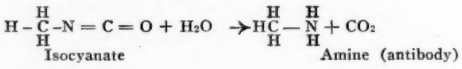
The isocyanide and carbon monoxide both carry a terminal pair of free bonds and similarly are toxic.

The unsaturated bonds of the isocyanide, in addition to combining with ammonia and amines, can also combine with oxygen, sulphur, chlorine and alcohol. The various derivatives would be represented by:



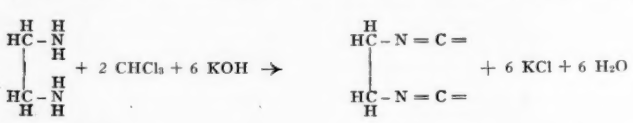
The therapeutic administration of oxygen and of sulphur in various forms has long been considered to have value in chronic infections; and alcohol has been used with good effects in acutely stricken persons. As here seen, alcohol has a direct combining value with isocyanide besides therapeutically making for vasodilatation and thus increased oxygen supply. All these substances have at least a transient power of neutralizing isocyanides (here put in parallel with toxins). They have nothing to do however with the mechanism of producing antibody.

In E. C. Rosenow's conversion of antigen to antibody, hydrogen peroxide leads to quickest effect. The oxygen converts the isocyanide to isocyanate, which then accelerates the production of amine.



EXPERIMENTAL

(1) Preparation of an Isocyanide as Antigen.—An isocyanide produced from ethylene diamine by the carbylamine reaction (known as the test for primary amines) yielded the garlic-odored isocyanide, ethylene diisocyanide.



In pharmacological tests, Rosenow found that 1/100 gm. of this impure product killed mice on intravenous injection, in one minute, through respiratory failure; 3/1000 gm. elicited violent respiratory movements followed by slight general spasms and a rapid and shallow type of respiration; 1/1000 gm. yielded these symptoms in milder degree, associated with much scratching of the head.

(2) Preparation of an Amine as Antibody.—A mixture of 1 c.c. of ethylene diisocyanide with 100 c.c. of water and 1.4 c.c. of concentrated HCl was refluxed in a flask for three hours. All odor of the isocyanide disappeared. The mixture was neutralized with NaOH solution, the hydro-

lytic product being an amine hydrochloride in physiologically normal salt solution.

(3) Preparation of an Amidine as an Immune Body.—The addition of ½ c.c. of ethylene diisocyanide (1) to 50 c.c. of the amine solution (2), shaken intermittently for twenty-four hours, made all odor of the isocyanide disappear. While the product of (1) killed mice within one minute, that of (2) antibody and (3) immune body proved harmless.

(4) Attempt at Chemical Analysis of Streptococcal Antigen and its Antibody.—A strip of moistened litmus paper, exposed to the distillation vapors when Rosenow's streptococcal suspension is evaporated to dryness on a steam bath, shows no color change upon the addition of 10 per cent NaOH solution. When the antibody is so treated, the indicator turns blue. In the latter case a volatile gas, ammoniacal or amine in type, has been formed and volatilized. This is what would happen if the toxin were an isocyanide and the antibody an amine.

I found that particles of zinc added to the alkalinized steam-bath-dried streptococcal suspension, in this experiment, brought about a hydrogenation, as evidenced by the giving off of an alkaline gas. This means that the toxin yields an amine upon reduction, further proof that an isocyanide was present in the original suspension.

If dilute sulphuric acid is used instead of NaOH solution, an acid gas is volatilized from the dried streptococcal suspension but not from the antibody. An isocyanide present (let it again be held in mind as antigen) should break up as follows, and this it does:

$$H-\overset{H}{\underset{H}{C}}-N=C=+\ 2H_2O\ (H_2SO_4) \rightarrow \underset{\text{Amine}}{H-\overset{H}{\underset{H}{C}}-\overset{H}{N}}\ \underset{\text{Sulphate}}{(\text{sulphate}} + \underset{\text{Formic Acid}}{H-C=O-OH}$$

The expected identification of the volatile acid is formic acid. I found the gas to be pungent and capable of decolorizing acidified potassium permanganate solution. The material involved is obviously a strong reducing agent. Formic acid is one of the best of these.

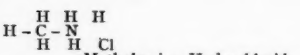
When Rosenow electrolyzed his antibody solutions, he noted an immediate release of an alkaline gas at the negative pole; his streptococcal suspensions (antigen), however, yielded such only much later. In the latter instance, the presumed chemical must first be formed through reduction by the liberated hydrogen before the alkaline gas can come into being. The chemical sequence is identical with that just described.

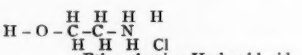
(5) Isolation of the Streptococcal Antibody.—This was attempted over two routes. As an amine, antibody should be sublimable as the hydrochloride from a steam-bath-dried sample. This was accomplished by covering the dried residue on a watch glass with a beaker, and heating on an electric plate. The sublimate consisted of crystals which had a build typical

of ammonium or amine hydrochloride. Rosenow tested solutions of these crystals to find that they agglutinated the streptococci as does the antibody itself.

Still better results were obtained toward isolation of the antibody by making the antibody solution slightly alkaline and by steam-distilling it. The distillate was caught in N/100 HCl and evaporated to dryness as the hydrochloride. It had the typical amine hydrochloride structure, identical with those obtained from the hydrolized or reduced product of the isocyanides. This product, too, had a high streptococcal agglutination power (1 :2500 as 2 plus ; 1 :3100 as 2 plus ; neither being toxic to mice—Rosenow).

(6) Various Simple Amines Tested for Antibody Effects.—N/200 solutions of the hydrochlorides of the following amines, in physiological salt solution, were submitted to Rosenow for testing: ammonia, methyl amine, di-*n*- propylamine, di-*n*-butylamine, tri-*n*-butylamine, ethanolamine and triethanolamine. Of these the hydrochloride of ammonia had no effect, but those of methylamine, di-*n*-butylamine, tri-*n*-butylamine and ethanolamine, in this order, showed increasing agglutinating power on several types of streptococci. Least toxic upon injection into mice, and of greatest agglutination power, were methylamine and ethanolamine hydrochlorides.


Methylamine Hydrochloride


Ethanolamine Hydrochloride

SUMMARY

Isocyanide structure is offered as the chemical characteristic of toxin; an amine derived therefrom, as antitoxin; the amidines resulting from combination of the two, as immune body. The organic cyanides were likened to carbon dioxide, as the isocyanides were likened to carbon monoxide. Attention was called to several addition reactions of the isocyanides other than those of the amines. An isocyanide as antigen, its derived amine as antibody, and the amidine as immune body, were made in the laboratory and tested for toxicity on mice. The outcome confirmed the expected. Chemical tests made upon E. C. Rosenow's streptococcal antigen and antibody gave evidence that the former contains isocyanide and the latter, amine. A substance with properties typical of an amine hydrochloride, and highly agglutinative, was crystallized from Rosenow's antibody. A short series of simple amine hydrochlorides was tested for antibody properties. Of the group, methylamine and ethanolamine hydrochlorides were found to be the least toxic and to exhibit the highest agglutinative power.

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CLINICAL OBSERVATIONS WITH THEPHORIN—A NEW ANTIHISTAMINIC DRUG

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WHEN Dale and Laidlaw, in 1910, pointed out the close resemblance between the effects of histamine injected intravenously into guinea pigs and the symptoms of anaphylactic shock, they laid the cornerstone for the histamine concept of allergy. Subsequently, a chain of experimental evidence was furnished by other investigators indicating that histamine or a histamine-like substance is the probable mediator of anaphylactic symptoms. However, attempts to build up an active immunity to histamine by giving gradually increasing doses of this amine to allergic patients have failed. Histamine-azoprotein also proved ineffective therapeutically. Similarly, histaminase, which destroys histamine *in vitro*, was disappointing clinically. Chemists have sought, therefore, for other substances which are capable of neutralizing the effects of histamine. Fourneau, Bovet, Halpern, and other French scientists found that certain phenolic ethers are potent histamine antagonists, but their early compounds proved too toxic for clinical use. Later it was demonstrated that Antergan and Neo-Antergan, both derivatives of ethylenediamine, are very effective in protecting experimental animals against histamine-induced bronchospasm and that they are less toxic than the original phenolic ethers. Both these preparations have been widely used in France since 1942 in the treatment of allergic disorders. In this country, Loew and his collaborators introduced another phenolic ether, Benadryl, and Mayer and associates produced another ethylenediamine, Pyribenzamine, and both these preparations established themselves promptly in therapeutics. However, many patients taking these drugs develop unpleasant side reactions, among which drowsiness and depression are most commonly encountered.

Therefore, pharmaceutical companies have continued to search for safe and effective antihistaminic drugs. Among the new arrivals, Thephorin* seemed of particular interest inasmuch as its chemical structure is radically different from that of the histamine antagonists previously reported. This compound, which was prepared by Wenner and Plati,[5] is chemically 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene hydrogen tartrate. The pharmacology of the stable, water-soluble, white powder has been adequately described by Lehmann. According to him,[3] Thephorin antagonizes important physiological actions of histamine in experimental animals; e.g., it prevents histamine-induced contractions of the smooth muscle of the bronchi and intestine; furthermore, it abolishes the effect of histamine on blood pressure and capillary permeability and it is of value in preventing

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*"Roche" brand of phenindamine. We are indebted to Dr. Leo Pirk of Hoffmann-La Roche, Inc., Nutley, New Jersey, for generous supplies of Thephorin.

anaphylactic shock. Acute toxicity studies, likewise according to Lehmann,[2] showed that in mice the LD_{50}** of Thephorin was about the same as that of Benadryl, but, by the intravenous route, the new compound proved only one-half to one-third as toxic as Pyribenzamine. There was no indication of chronic toxicity of Thephorin in either rats or dogs.

With this evidence of antihistaminic activity and of comparatively low toxicity, we embarked upon clinical trials.

The case material consisted of seventy-six adult patients complaining of symptoms which were either proved or thought to be of an allergic nature. The types of cases included nasal allergies, both of the seasonal and non-seasonal variety; bronchial asthma, urticaria, and migraine. However, only patients with a diagnosis of hay fever and asthma were represented by sizable numbers. All subjects had been given hyposensitization treatment but were not adequately relieved . Thephorin was administered in 25 mg. tablets. These were prescribed on a three-times-daily basis. In some instances, the daily dose was increased to 100 mg. As relief was obtained, the dose was generally reduced with the object of establishing a maintenance dose.

Side effects occurred in five patients. They all complained of insomnia and one of them also of nausea. These reactions were not severe and abated promptly on discontinuation of the drug. None of the subjects studied experienced drowsiness or depression. Two patients received a daily dose of 75 mg. of Thephorin for three months. Physical examinations, urinalyses, hemograms, and electrocardiograms done for these subjects before, during and at the end of the three-month period failed to reveal any evidence of toxic effects.

TABLE I. RESULTS FROM THEPHORIN THERAPY IN 76 ALLERGIC PATIENTS

Diagnosis	Cases	RESULTS Good	Fair	Negative
Hay Fever	41	18	4	19
Bronchial Asthma	26	9	4	13
Vasomotor rhinitis	6	0	3	3
Urticaria	2	2	0	0
Migraine	1	0	0	1
Totals	76	29	11	36

The results obtained are listed in Table I. It appears that of the forty-one patients with hay fever, twenty-two were benefited, with eighteen deriving good relief and four fair relief, and nineteen were not improved. Furthermore, it can be seen from the table that of the twenty-six patients suffering from asthma, thirteen were relieved and thirteen were not benefited. It is interesting to note that the asthma cases which were improved were inhalant patients whose sinuses did not reveal any pathologic basis. On the other hand, seven of the thirteen asthmatics deriving no benefit showed nasal pathologic conditions. Of the six subjects with a diagnosis of

**LD_{50} is defined as the dose which is lethal for 50 per cent of the animals used in the experiment.

nonseasonal vasomotor rhinitis, three derived some degree of benefit and three were not improved. The two cases of urticaria obtained good relief, but the patient suffering from migraine was not benefited.

COMMENTS

While the series presented is small, the results obtained indicate that Thephorin is an effective histamine antagonist. Since side reactions are negligible, Thephorin can be used with impunity in patients who do not tolerate Benadryl and/or Pyribenzamine. In fact, it may be advantageous to try Thephorin initially, thus sparing many a patient the trouble of experiencing the unpleasant reactions which are so commonly encountered with the antihistaminics of the older type.

Reynolds and Horton[4] have recently presented their findings with Thephorin. They reported sixty-two patients, of whom thirty-nine were benefited. Of the seventy-six patients we studied, forty derived benefit. Thus, our results are somewhat less favorable than those of Reynolds and Horton. This may be due to the fact that they used somewhat higher doses of Thephorin. However, we are in complete agreement with these authors that Thephorin is distinguished by low toxicity. Similarly, Criep[1] states that, "Unlike the other drugs, it" (sc. Thephorin) "does not produce drowsiness and sleepiness."

It must not be forgotten, though, that all antihistaminic drugs are only palliatives. None of these preparations will relieve the physician from attempts to recognize the offending allergen and to eliminate it or to hyposensitize the patient. The antihistaminics have a place in conjunction with the orthodox therapy when the latter does not adequately control the symptoms or before it brings relief to the patient.

SUMMARY AND CONCLUSIONS

Seventy-six patients complaining of various allergic manifestations were treated with Thephorin, a new antihistaminic drug, which belongs to a heretofore unknown class of compounds.

The results obtained are presented in tabulated form. The almost negligible side effects appear to be an attractive part of the new compound. In particular, it is not conducive to drowsiness. It is concluded that Thephorin is a useful drug in the symptomatic treatment of allergic conditions.

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ADEQUATE DIETS IN ADVANCED CHRONIC ASTHMA

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MALNUTRITION among patients with advanced asthma is common. Rackemann[1] employed the term "depletion" in elaborating on this clinical feature of chronic asthma. Without presenting clear evidence of a lack of individual metabolic constituents, he believes that there must be serious deficiencies in these patients because of their malnourished and debilitated appearance. There is no proof at this time that such deficiencies exist, except that during an acute attack of asthma considerable loss of water takes place (Stoesser,[4] Sheldon[3]). When this occurs frequently, it might perhaps contribute to some loss of weight.

More significant, however, is the fact that many patients are following inadequate diets. The fear of experiencing an ill effect from eating certain foods often induces the patient to avoid these foods for months or even years, contrary to medical advice.

It is generally accepted that diets are essential in the treatment of asthma. The majority of allergists employ temporary, others more or less permanent, elimination regimes which are usually based on skin tests. Others use such standard elimination diets as the ones advocated by Rowe.[2] Others eliminate empirically certain foods which are thought to be frequent sources of asthmatic attacks, such as milk, wheat or eggs. This is subsequently followed by gradual addition of the eliminated articles.

Only a few disregard food sensitivity altogether and advise their chronic patients to eat whatever they desire. In order to investigate this latter, rather unconventional procedure, a series of patients with advanced chronic asthma who were markedly undernourished were placed on an adequate and high caloric diet, disregarding entirely their sensitivities to foods as determined both by clinical observation and by skin tests.

We were concerned with two questions: (1) In what proportion of cases would the asthma become either aggravated or ameliorated? (2) How would this diet affect the patient's nutritional state?

METHOD

Fifty-six* patients were selected for this study on the basis of their being below their optimal weight and of having chronic asthma which was proven to be of allergic origin and uncomplicated by such secondary changes as bronchiectasis or pneumonitis. All patients exhibited positive skin reactions to foods as well as to other substances. The duration of their disease ranged from one to twenty years. Six patients had had no previous

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*Including seventeen children below fifteen years of age.

treatment in our office, while fifty had been under observation and treatment for several months or years. At the time when this study was started, their disease had shown no tendency toward improvement. While the observations concerning the diet were carried out, no change was made in the patient's routine. The new patients received no treatment other than the diet, but were instructed to abide by the routine which they had followed before they came under our care. The diets ranged from 2,000 calories to 4,000 calories, the average being 2,600 calories. The adequacy of the caloric intake was judged by the patients' weight; an effort was made to have them attain the "ideal" weight for their age and height.† Emphasis was placed on inclusion of all foods which had formerly been eliminated.

It has been our experience that any ill effect derived from food to which sensitivity exists, becomes manifest within several hours after its ingestion. Conversely, any mode of treatment, if effective in chronic asthma, should accomplish results within a day or two after its initiation. A period of close observation of two weeks, therefore, was considered appropriate for our purpose. During this interval the patients were seen every second day; they were then followed up weekly or bi-weekly for at least three months.**

Careful records were kept on three points: (1) the number and severity of attacks before and after the diet was instituted, (2) the gain or loss of weight while following the diet, (3) the patient's own impression of the effect of the diet on his general health.

Before discussing our results, it is of interest to review briefly some of the data obtained from the history taken by the dietitian (MMH) for the purpose of evaluating the patients' diet prior to the two weeks' period of observation. Of the fifty-six patients, only thirteen had not been restricting their food intake; forty-three (including fourteen children) had been adhering to some form of elimination procedure, ranging from avoidance of a few individual items which they themselves considered harmful, to strict elimination diets prescribed either by ourselves or by other physicians. While these diets had been planned to be of sufficient caloric value and to be adequate in vitamins and other food essentials, they actually were lacking considerably in this respect. In thirty-eight of the forty-three patients there was a history of sensitivity to certain foods, yet in twenty-nine, the elimination procedures had not contributed perceptibly to the control of asthma; four were under the impression that food elimination had aggravated their disease. However, six of the forty-three patients had noted a general improvement of their asthmatic state, and four had been temporarily better on food elimination. In some of these individuals, considerable persuasion was required to induce them to follow the new dietary regime.

The average weight below the optimum for their height and age in the

†The food groups listed in the "basic seven" recommended by the National Research Council served as a guide to evaluate the patients' food intake.

**Extending from mid-July through October, 1946, a period which coincides with the late grass and ragweed season.

fifty-six patients was 8.1 kg. The dietitian's history indicated that there had been a very conspicuous lack in daily caloric intake in thirty-eight patients and a striking deficiency in protein intake in the diet of thirty-one. Two of these individuals presented edema about the ankles and eyes, which was believed to be due to nitrogen deficiency. In sixteen patients, vitamin deficiencies were suspected because of such manifestations as dryness of the skin, bleeding gums, dryness of the tongue and lips, and paresthesias in the extremities.

RESULTS

Fifty patients were able to tolerate the diets without ill effect. Three of the remaining six suffered severe attacks of asthma when they attempted to eat the added foods which had previously been eliminated; they were obliged to give up further efforts to follow our regime. The other three succeeded in following the diet in spite of several unsuccessful attempts. While following the diet for two weeks they developed such symptoms as rhinorrhea, nasal blockage, minor asthmatic seizures, headache and general weakness. In one patient, marked flatulence and gastric discomfort occurred.

The average gain in weight in forty patients was 1.52 kg. during the two weeks' period. In ten there was no change, and in the three who developed untoward symptoms, there was an average loss of .75 kg. One patient (Mr. A. S.) gained 3.4 kg. on a diet of 4,000 calories. In conjunction with the gain of weight, they noted a general subjective improvement, a return of their physical strength and a great change in their mental outlook.

As to the effect of the diet on the asthmatic attacks, there was an aggravation in the three individuals as noted above; no change was detectable in ten, while in forty the number and severity of the seizures lessened appreciably. Of this latter number, twelve patients remained free from attacks for more than three months. The improvement in the patients' nutrition paralleled strikingly that of the asthma.

The following two case reports present typical examples illustrating the manner in which the patients responded to the diet.

CASE REPORT

Case 1.—Mrs. L. C. L., aged thirty-seven, had been under our care since March, 1938, having been afflicted then with bronchial asthma for one year. At first, the attacks were present perennially, with some aggravation during and following each ragweed season. They ceased completely from June, 1943, until February, 1945. Since then she suffered daily attacks except for brief periods while she was hospitalized. During the past three months the seizures had become so severe that they did not yield to the usual symptomatic treatment (aminophylline, ephedrine, epinephrine). The patient had experienced sensitivity to various foods, especially to certain meats, fish and eggs, which she had been avoiding. She also had noted sensitivity to house dust. Intradermal skin tests in 1938, in 1945 and in 1946

revealed major reactions to these substances as well as to ragweed, grass pollen, and several fungi. There were other reactions to numerous foods and inhalants.

The physical examination revealed an underdeveloped and emaciated white female with considerable dyspnea, her weight being 47 kg., the estimated weight for her age and height being 57.5 kg. There was no evidence of infection in the nose and sinuses; the nasal membranes exhibited a typical allergic appearance with considerable edema and pale, bluish discoloration. The chest findings were characteristic of advanced asthma with marked emphysema and a tendency to pigeon chest. X-ray and blood studies were negative except for a blood eosinophilia of 12 per cent.

The patient had been receiving injections of pollen, fungi and other inhalants to which she was sensitive. She had been on elimination diets of Rowe, and on other occasions on strict avoidance of the large variety of foods to which she had reacted on skin testing in 1938 and 1945. Her daily caloric intake was estimated at between 1,400 and 1,900 calories.

On July 27, she was asked to disregard all former food sensitivities and follow a full diet of 2,600 calories. Within twenty-four hours she reported that she was able to sleep through the night for the first time in months. At the end of the first week she had gained 1.1 kg. Her asthma had ceased entirely during the day, and minor attacks, occurring only at nighttime, were readily controlled with ⅜ grain of ephedrine sulfate and 1½ grains of aminophylline. The hyposensitizing injections were carried on at weekly intervals throughout the ragweed season. The patient was entirely free from asthma until December 24, 1946, when she developed slight wheezing following an upper respiratory infection. This cleared up spontaneously within two days. On January 24, 1947, she had still been free from wheezing; her weight was 56 kg. and she had been in the best of health.

Case 2.—Miss M. W., aged twenty-nine, had been under our observation for seven years. She had been one of the most intractable cases encountered in our practice. The asthma began in 1939 at the height of the timothy season. At first, there had been brief periods of freedom from attacks; since February, 1943, however, the attacks had been present more or less continuously. Practically every night she had to resort to inhalation of epinephrine and occasionally to hypodermic injections ranging from 0.1 c.c. to 0.2 c.c. Repeated physical examinations, several rhinological, bronchoscopic and x-ray examinations revealed entirely negative findings except for the presence of emphysema and the physical signs in the lungs of uncomplicated bronchial asthma.

According to her history, milk, all fowl, most nuts and beans disagreed with her. She had attempted to avoid these foods for years, paying particular attention to such avoidance when there was an aggravation of her attacks. However, the intradermal skin tests done in 1943 were entirely negative. When repeated in September, 1945, and again in June, 1946, they showed strongly positive reactions to a large variety of antigens of all types. These reactions varied greatly upon each testing. The elimination diet based on these tests, as well as injections of pollen, fungi and house dust failed to produce results. On one occasion intramuscular injections of milk (0.2 to 1.0 c.c. daily) brought about complete relief from asthma for five days, but were ineffective on subsequent trials. Milk had been the only food which had given constantly strong positive reactions on repeated testings.

On August 7, 1946, when her weight was 51.5 kg., the patient was given a diet of 2,600 calories, disregarding all food sensitivities. Within forty-eight hours she reported marked relief from asthma; within a week she became entirely free from attacks, and had gained 1.9 kg. Subjectively, she felt better than at any time during the past three years. This improvement lasted for six weeks, during which the hyposensitizing injections were carried on in the same manner as before. Then,

slight attacks began to recur every second to third night, which were readily controllable by 1½ grains of aminophylline orally. In mid-November, this condition became aggravated by what appeared to be an upper respiratory infection with fever up to 101°. The attacks have appeared more frequently since, but have been much less severe than at any time since the patient came under our observation. Her weight on February 1, 1947, was 62.2 kg.

COMMENT

These two cases were selected here because they constitute typical instances of the forty patients who benefited from the diet, from the point of view of severity and chronicity of the disease. They also illustrate how the benefits from the diet were maintained; twelve patients have actually become entirely free from asthma as in Case 1, while others have experienced a relapse into the asthmatic state. But even in the latter group, marked general improvement persisted for a long time. Because of the well-known difficulties encountered in maintaining a critical judgment in interpreting results in chronic asthma, no further elaboration on the degree and permanency of the improvement is made here. Case 2 furthermore illustrates a common observation concerning food sensitivity, namely, that reactions to foods, in contradistinction to those to pollen and other inhalants, do not tend to remain constant on repeated testing. Similarly, foods which account for asthmatic attacks on one occasion may be eaten with impunity at other times.

DISCUSSION

While no attempt is made here to present statistical data, certain reasons lead one to expect that advanced chronic asthma is frequently accompanied by malnutrition. Asthmatic attacks often interfere with the process of eating through the embarrassment in breathing. Sometimes the slight exertion required for eating seems to aggravate attacks, thus deterring the patient from eating properly. Furthermore, the drugs usually employed for asthma (as ephedrine, the new antihistamine drugs, and aminophylline) may induce gastrointestinal disturbances and thus interfere with appetite and digestion. The chief reasons, however, for the patients' malnutrition, judging from our observations and from discussions with the individual patients, is their anticipation of developing asthma if they eat certain foods. This fear is based largely on their own unpleasant experience of having suffered attacks from foods to which they had been sensitive at one time. Sometimes the physician who places too much emphasis upon food sensitivity enhances the patient's concern about foods. A great deal of persuasion is often necessary to have them follow a more adequate dietary regime once they are in the possession of an elimination list.

Only six patients could not tolerate a diet containing the foods to which they had been clinically sensitive or which had given positive skin reactions. This indicates that food does not play a major part in the majority of the patients with asthma, an observation which is in striking

contrast with the views of many allergists. Yet, it also suggests that in a few instances, approximately 10 per cent, food cannot be disregarded as a major cause of the attacks. In young children and infants, who were not represented in our group, food undoubtedly is of greater importance than in adult asthmatics.

In view of this discrepancy of opinion concerning the role played by food in chronic asthma, one wonders to what extent psychogenic factors enter into this subject. In watching these patients closely, we were indeed reminded of the startling "cures" of asthma effected by certain charlatans. One of us (GLW) has had occasion to analyze the detailed "case records" of such "cures." Most of the patients had been urged by the "doctor" in question to disregard all food sensitization. There are many reasons[5] for an individual afflicted with chronic asthma to develop a psychosomatic aggravation of the disease which may in time become its dominant feature. By the same token, the reverse may hold true, namely that the startling results which are so often encountered from strict elimination diets may in a few instances be effected by the patient's attitude.

This theory, however, is not sufficient to explain our results. In view of the remarkable parallelism in the amelioration of the asthma and the gain in weight, we cannot help but feel that the malnutrition itself and the inherent "depletion" in essential food elements constitutes the major issue in the persistence of the asthmatic state. The addition of these foods may therefore assist in re-establishing the "allergic balance," thus aiding the patient in overcoming the attacks.

SUMMARY

1. Fifty-six patients with chronic asthma who were on an average of 8.1 kg. below their estimated weight were placed on diets adequate in calories and in all essential food constituents, disregarding entirely existing food sensitivity.

2. All patients had given positive skin reactions to foods; in thirty-eight the history indicated sensitivity to certain foods. Forty-three had previously been on food elimination regimes with the following results: twenty-nine believed that such diets had had no effect on the course of the asthma; four had noted an aggravation; and ten had experienced temporary improvement of the asthmatic state.

3. The history and examination findings suggested deficiency in protein and vitamin intake in thirty-one patients.

4. Fifty of the fifty-six patients were able to tolerate the diet without ill effect; three developed such severe asthmatic attacks that they had to abandon the diet. Three others were able to follow it during the two weeks' trial period, but suffered some untoward symptoms from the diet.

5. In forty patients the average gain in weight was 1.52 kg.; in ten the weight remained stationary, and in the three who developed untoward

symptoms, there was an average loss of .75 kg. The effect on the asthma paralleled closely the patient's improvement in nutrition. Of the forty patients who were temporarily relieved, twelve remained free from attacks for more than three months.

6. In explaining these results, it is suggested that the deficiency in essential food constituents and in caloric intake ("depletion") contributes to the persistence of the asthmatic state. Psychosomatic factors cannot be excluded.

CONCLUSION

It is concluded that patients with chronic asthma who are undernourished may derive great benefits, with respect to their asthma and their general health, from diets adequate in all essentials and of sufficient calories to maintain a normal weight, regardless of the fact that these diets contain foods to which positive skin reactions are obtained and to which the patients had previously reacted clinically. Such diets, however, should be planned judiciously, since approximately 10 per cent of these individuals may experience some ill effects.

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SENSITIZATION TO PETROLATUM IN OINTMENT BASES

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SENSITIZATION to medicaments used in ointments for the treatment of dermatitis is met with frequently. It is well recognized that such superimposed sensitivities are complicating factors in many of the allergic dermatoses. Long after the primary factor is removed, a dermatitis may persist because of the application of some item in the local treatment to which secondary sensitivity has occurred. Many physicians, with this possibility in mind, routinely eliminate all previous local treatment at the onset of the study of a case of allergic dermatitis, and mild lotions or simple emollients are frequently prescribed. In many such patients one is struck by the immediate initial improvement which frequently occurs, which can only be attributed to the elimination of some irritant present in the previous local treatment. Most clinicians rightly attribute such improvement to the elimination of the medicaments previously used, but overlook the possibility that petrolatum and related substances, the commonest constituents of ointment bases, may cause such sensitivity.

Many of the patients with chronic dermatitis presenting themselves for allergic study have been under treatment for months or years. These patients have had many ointments prescribed, the medicaments of which have varied from physician to physician. The ointment bases in such prescriptions almost invariably contain petrolatum in one form or another.*

It is well known that sensitivity may be acquired more readily through the broken than through the normal skin. The conditions for the acquisition of secondary sensitivities in cases of dermatitis are ideal, i.e., the repeated and frequent application of a substance to the broken skin over a long period of time. It is not surprising, therefore, that under these conditions sensitivity to medicaments is frequently encountered. However, judging from the paucity of reports in the literature, it is surprising that sensitivity to petrolatum is apparently of rare occurrence. It has been held that such

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*The following common ointment bases contain petrolatum or mineral oil, according to personal communications from the manufacturers. Many others undoubtedly contain these substances.

Vaseline—White or yellow.
Qualatum (Polyhydric fatty acid esters in petrolatum. Almay)
Aquaphor (Alcohols and esters of cholesterol derived from wool fat, 6 per cent in petrolatum. Duke Laboratories)
Unibase (Parke-Davis & Co.)
Greaseless Ointment Base (Burroughs-Wellcome & Co.)
Hydrosorb (Abbott)
Albolene and Albolene Cream (McKesson)
Dermovan (Texas Pharmacal Co.)

Most of the so-called nonallergic or hypo-allergic cosmetic creams contain considerable petrolatum or mineral oil.[3]

Many of the newer emulsion bases contain mineral oil. However, one of these, Almay Emulsion Base, is said by the manufacturer to be entirely free of petrolatum and mineral oil. Several of the ointment bases mentioned above are said to be prepared from highly purified petrolatum or mineral oil, and theoretically should be less irritating to petrolatum-sensitive patients. That such is possible is exemplified by Case 2, able to tolerate Qualatum (Almay) and not Albolene Cream.

sensitivity is an infrequent possibility because petrolatum is such a mild substance. In one of the few reports in the literature of sensitivity to pure petrolatum, Hollender[1] states that it is a very poor sensitizer; and even though it is the most widely used ointment base, he was unable to find previously reported cases of sensitization. His case was one of severe dermatitis of the face due to petrolatum applied to the scalp. He obtained a positive patch test by rubbing the material into the forearm four times a day for several days. It required three or four days to produce a positive reaction, which was characterized by a pin-point pruritic vesicular eruption.

Niles[2] reported a case of dermatitis which he proved was due to liquid petrolatum used in a hair tonic. Prior to these reports, Webber,[5] who had compiled a very comprehensive list of external causes of dermatitis from which petrolatum was excluded, commented on this point, "The literature fails to show reports of dermatitis from pure petrolatum because it is one of the most stable bodies and does not contain phenol, cresol or any saponifying matter." Hollender[1] discussed Webber's statement in his paper, and stated that, "This is unquestionably true, for otherwise cases would have been observed and reported, as petrolatum is one of the most widely used ointment bases."

No additional cases of sensitivity to petrolatum have been reported. Sulzberger[4] lists it as a possible irritant. The view of most allergists and dermatologists is that impure petrolatum products may cause dermatitis, such as found among individuals working with machine oils, but sensitivity to the purified materials, as used in ointment bases, occurs with extreme rarity.

Patch tests on normal skin, even with not too highly purified yellow petrolatum, rarely produce a positive skin reaction. Hollender's case gave a positive reaction only after several days of rubbing the material into the skin four times a day. The rarity of reports of petrolatum sensitivity is no doubt partly due to the difficulty in obtaining positive patch reactions to this substance. For this reason, we have relied on the so-called "usage test" in investigating this problem. Our procedure is to supply the patient with small tins of white and yellow petrolatum, anhydrous lanolin, and benzoinated lard. He is instructed to rub each ointment base into different affected sites, each one for several days at a time, noting any exaggeration of the amount of itching and local irritation produced. A small area the size of a 50-cent piece is sufficient for test purposes. The "usage test" can be carried out in any affected area, but the more sensitive sites are the flexural surfaces of the knees and elbows, and the skin above the suprasternal notch and eyelids. A reaction is considered positive when, following the application of any of these materials, itching and erythema are increased. In some of our cases, itching began at the site of a usage test within fifteen minutes or less. Others did not show any irritation until after the application of the material several times a day for several days. Many patients who claimed that, "Any greasy

substance makes me itch," were found sensitive to petrolatum and not to lanolin and lard, and were able to tolerate the latter substances.

There are undoubtedly a number of patients suffering from dermatitis who are unable to tolerate any greasy substance on the skin. Many such cases may be found sensitive to one of the ointment bases by means of the usage test. Most patients, whom we have found sensitive to an ointment base in this series, were sensitive to petrolatum. A few were sensitive to both petrolatum and lanolin; several were sensitive to lanolin alone. In none have we found a sensitivity to benzoinated lard. The latter substance, however, is very drying and is far from the ideal substitute for petrolatum. As a substitute for a petrolatum-containing ointment base we have found useful an emollient composed of lanolin and/or benzoinated lard combined with Almay Emulsion Base.

REPORT ON CASES

Case 1.—Mrs. H., aged twenty-nine, had dermatitis of the upper eyelids and neck of six months' duration. The patch reaction to her nail polish was positive. The dermatitis cleared up partially following the elimination of the nail polish. A number of weeks later there was still itching, redness and scaling of the affected areas.

All previous local treatment and cosmetics had been eliminated except albolene which was used to allay the dryness and the tendency to scaling. The emollient cream containing benzoinated lard and emulsion base was substituted for the albolene. The condition cleared up completely within a few weeks. Subsequent trial with petrolatum, mineral oil and albolene at intervals extending over several years always reproduced itching and redness of the eyelids. It was never possible to obtain a positive patch test by rubbing these substances into other areas of the body.

Case 2.—Mrs. P., aged forty-two, had severe dermatitis of the eyelids for nine months. The lids were dry, itchy and scaly. There was considerable blepharitis with occasional acute attacks of conjunctivitis. Previous elimination of all cosmetics, creams and nail polishes for several months were without benefit. During this interval the substitution of several brands of "nonallergic" cosmetics and creams produced no change in her condition. The patient was given only white petrolatum to control the severe dryness and scaling of the lids. She stated that following the application of the petrolatum the lids were soothed for several hours and then began to itch again with great intensity. Qualatum, although containing petrolatum, did not produce itching, the petrolatum in this preparation apparently being highly refined and not containing the substances irritating to the patient. A cream composed of Qualatum and emulsion base was substituted for the petrolatum. Within a few days the condition began to clear up; at the end of two weeks it was completely healed and has remained so for over one year. The patient has continued the use of this cream as a substitute for her cosmetic creams.

Case 3.—Mrs. B. H., aged thirty, had suffered from a severe dermatitis of the face, neck and extremities all her life. There was a very strong past and family history of allergy, chiefly asthma and hay fever. Several previous allergic studies and subsequent desensitization resulted in variable and incomplete benefit. When first seen, the dermatitis was very violent and acute. The itching was intense, and the patient at times seemed on the verge of a nervous collapse. Sedatives and the liberal use of antihistaminic agents gave only slight relief. She was applying yellow petrolatum freely as a soothing application. As long as this substance was

applied, the tendency to scaling and dryness was overcome, but the itching continued intensely. All previous local medicaments had been eliminated by her dermatologist.

Complete allergic studies were initiated, followed by an elimination and desensitization program. In the meantime, various local medicaments were combined in the special emollient cream mentioned above to allay the itch. It was found by the usage test that this patient was intensely sensitive to Vaseline and lanolin. She was unable to tolerate some of the newer ointment bases containing petrolatum or mineral oil. The persistence of her condition was undoubtedly due to these substances. Several months of both systemic and local therapy, the latter consisting of mild local applications of petrolatum-free and lanolin-free ointments, resulted in almost complete clearing of this condition for the first time in many years. One year after the initial examination the patient was having only occasional mild flare-ups and was leading a normal social and domestic existence. Patch tests with both lanolin and Vaseline on unaffected sites were negative, despite repeated thorough application. However, usage tests after several days on previously affected areas were still slightly positive.

Case 4.—Mr. G., aged sixty-six, was a cobbler who developed a severe, pruritic dermatitis of his fingers and hands extending on the flexural surfaces of the arms to the elbows. The condition had persisted for about three months. During this time he had used various ointments some of which he thought aggravated the itching. During a week out of the city, he cleared partially, but still itched severely at times. He continued the use of several of his ointments during this interval.

Allergic study of his case revealed a very strongly positive patch test to a brown ink used for dyeing the edges of new soles. Usage tests for white petrolatum and for several ointment bases that contained petrolatum were positive. Some of these produced itching within a few minutes after they were applied to affected areas. Patch tests on normal skin with these substances were negative. He was able to tolerate lanolin without difficulty.

The skin condition cleared up completely within a few weeks following the elimination from his shop of the incriminated brown dye. During this time he used lanolin exclusively for local treatment.

Case 5.—A. B., aged seven, had had facial eczema during infancy, and chronic atopic eczema of the flexural surfaces of the knees and elbows of three years' duration. Complete skin testing revealed sensitivities to numerous foods and inhalants, elimination of which produced only partial relief. Usage tests showed marked sensitivity to white petrolatum and several petrolatum-containing ointment bases. Patch tests for these items were negative. Petrolatum-free ointments were prescribed for local treatment, continuing the elimination and desensitization regime. The condition cleared up rapidly and completely. Some months later, the repeated application of petrolatum to the previously affected areas did not reproduce itching or irritation.

Case 6.—Mrs. G., aged thirty-five, was under treatment for seasonal and perennial hay fever. She developed a severe irritation of both her lips. She did not recall any recent change in her lipstick or cosmetics. Several "nonallergic" lipsticks were tried all of which produced irritation of the lips. The cheilitis required from one to three weeks to clear up after each relapse. Patch tests with a number of the dyes and other ingredients used in these lipsticks were negative. During an interval of freedom, white petrolatum and lanolin were applied in turn to the lips. Each of these usage tests was positive within a few days. Subsequently a lipstick was obtained for this patient containing neither lanolin nor Vaseline.† She was able to use this lipstick without return of the cheilitis.

†Lipstick No. 200, Ar-Ex Cosmetic Company, Inc., Chicago, Illinois.

DISCUSSION

In addition to the six definite cases of sensitivity reported above, several patients have been encountered during the last few years in whom a less definite allergy to petrolatum was suspected. These cases complained of itching after the application of ointments. Usage tests were questionably positive, and the results were too indefinite to include in this report. However, it may be worth while to note that these individuals seemed to do better, and were more comfortable, on petrolatum-free ointment bases. Several were better able to tolerate the newer ointment bases said to contain more highly purified petrolatum or mineral oil.

Sensitization to petrolatum, mineral oil and related substances used in ointment bases must occur more frequently than generally suspected. Otherwise, one observer would not be likely to see such a disproportionate number of cases. The probable explanation of the rarity of previous reports is the fact that reliance for diagnosis has been placed on the patch tests. It should be emphasized that substances as mild as these rarely react to patch tests even when the material is repeatedly rubbed into the normal skin. The usage test is of the greatest value for such substances. By means of this method, the ability of the patient to tolerate these and other medicaments can be rapidly determined, and the diagnosis of sensitivity to various ointment bases can thus be made when suspected.

SUMMARY

1. Many ointment bases contain petrolatum or mineral oil.

2. Six cases of definite sensitivity to petrolatum or related substances are reported.

3. Patch tests on normal skin for purified petrolatum are rarely positive.

4. Usage tests are a valuable means of making a diagnosis of petrolatum sensitivity. These may be positive on affected sites and later negative on the same healed sites.

5. In view of the widespread use of ointment bases containing petrolatum and/or mineral oil for the local treatment of the allergic dermatoses, the possibility of sensitization to these items should be kept in mind.

* * *

Since this paper was submitted for publication, we have encountered four additional cases definitely sensitive to petrolatum. These were all negative to patch tests, and positive to the usage tests carried out on the affected sites.

One was a case of cheilitis sensitive only to petrolatum and to none of the other lipstick ingredients. The second was a case of seborrheic eczema in a patient who failed to clear despite adequate local therapy until mineral oil was interdicted for local application. The other two cases were typical chronic atopic eczema in children who had failed to respond to the usual allergic studies and desensitization treatment until petrolatum-free ointment bases were prescribed.

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A STUDY OF ATOPIC ECZEMA

I. Further Observations on Allergy to Human Dander
II. Cutaneous Reactions to Eczema Scales

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IN previous communications[2–6] on the subject of atopic eczema,* a report was made of the occurrence of cutaneous reactions to human dander in patients with this disease. These reactions consisted of (1) urticarial reactions to scratch test, obtained in older children and adults; (2) eczematous reactions to patch test on normal skin, obtained in a large percentage of children and a small percentage of adults; (3) eczematous reactions to massage or inunction test, which closely paralleled the patch tests on normal skin, and (4) eczematous reactions to patch test applied on scarified skin, obtained in adults (and also obtainable in children).

The hypothesis that human dander is an important allergenic excitant of the disease was stated to rest upon the following evidence: (1) All persons have contact with human dander from their own scalps or from those of others about them, or both. (2) A large percentage of persons with the disease exhibit cutaneous reactions to human dander, whereas in persons without the disease such reactions occur only rarely. (3) The reactions to patch test on normal skin and on scarified skin and those to massage or inunction are eczematous reactions and reproduce the lesions of the disease. (4) Avoidance of human dander is of value in treatment of the disease. (5) The location of the lesions on the face, neck, flexure surfaces such as the cubital space, the upper arm below the lower margin of the sleeve (in children with short sleeves), the cheeks and chin may *partially* be explained on the basis of such factors as proximity to the scalp, exposure to contact with human dander from the parent's head, neck and shoulders, solution and penetration of dander allergen in areas of flexion, et cetera. (6) Scratching is harmful not only because of mechanical injury to the skin but also because the finger nails, due to their frequent contact with the scalp, inoculate the skin with dander allergen.

I. FURTHER OBSERVATIONS ON ALLERGY TO HUMAN DANDER

The weakest link in this chain of evidence is item No. 4, which is concerned with the value of avoidance of dander in treatment of the disease. In the previous report (on this aspect of the problem) evidence was based on the favorable results obtained in three of four cases.[4] Since

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*In other publications on this subject the author has used the terms:
1. "Atopic eczema" synonymous with "atopic dermatitis."
2. "Eczematous reaction" synonymous with "characteristic atopic reaction to patch test."
The reason for using different terms in different publications on the same subject is that various editors require the use of certain terms as a prerequisite of publication.

this is an extremely small series and because atopic eczema is capricious in its manifestations, it was considered desirable and necessary to make further careful clinical observations on a larger series of cases, both children and adults. These observations were made during the colder months of the year, October to May, because in a large proportion of the cases the disease improves or disappears in hot weather. Hence, any methods of treatment, begun in May or June and continued for several months, is likely to be erroneously regarded as effective. With one exception these patients were treated in the home. In the selection of cases for study, prime consideration was given to obtaining those patients who (themselves or their parents) gave promise of co-operating reasonably well.

The plan of study included the usual history, physical examination, routine cutaneous tests (scratch method) with foods and inhalants, and patch tests (on normal and on scarified skin) with human dander. These were followed by a preliminary observation period of variable time, usually several weeks. During this period the only local remedies used were cold cream, zinc oxide ointment and calamine lotion. These were used also during the subsequent period of study. During this period an attempt was made to diminish the patients' contact with human dander and to evaluate the effect of such diminution on the clinical course of the disease.

Avoidance of human dander, because of the ubiquity of the substance and its intimate association with human beings, was necessarily incomplete. However, a study of the reactions to patch and inunction tests suggests that an avoidance, even though incomplete, might be of considerable value in treatment, provided that human dander is a major factor in the pathogenesis of this disease and provided it acts through *surface contact* with the skin. The reason for this opinion is that a relatively great exposure is necessary to produce reactions to patch or inunction tests. These reactions, for example, are not nearly of the degree of magnitude of those produced in contact-type eczema by such substances as mercury, nickel, poison ivy, et cetera.

Diminished contact with human dander was to be accomplished by frequent washing of the scalp with soap and water, wearing long sleeves and high-neck dresses, frequent changing of clothing, frequent changing of pajamas and bed linens, wearing long-sleeve pajamas, having parents avoid contact of the child with their face, neck, hair and shoulders, having parents of eczematous children wash their own scalps frequently, enclosing the hair by wrapping with cloth. One child, Case No. 4, was removed to a hospital to avoid her mother's dander. In another Case, No. 11, the hair of the scalp was cut short to facilitate cleansing.

Observations were made on fourteen patients, eight of whom were less than four years of age, the remaining six being nine to thirty-six years of age. All except three were allergic to human dander. These three latter cases were included in the study as "negative" controls.

CASE REPORTS

(Concerning the term "E.M.Z. eczema scales," see Part II)

Case 1.—G.S., a boy, aged two, had eczema of twelve months' duration, on the face, forearms and cubital spaces. The eczema was definitely worse in the winter and better in the summer. His mother had perennial hay fever. Urticarial reactions to scratch tests: ragweed pollen, ++; foods, negative. Eczematous reactions to patch tests: human dander, ++; E.M.Z. eczema scales, ++; ragweed pollen, +++. In spite of careful avoidance of human dander, as thoroughly as could be accomplished in the home, his eczema continued without much change throughout the winter and spring. During the ragweed season in August and September there was no exacerbation of the eczema.

Case 2.—B.S.L., a girl, aged two, had eczema of the face, hands, wrists, forearms, cubital and popliteal spaces of twelve months' duration, present all year but worse in the winter. Her great grandmother had asthma. Urticarial reactions to scratch tests: egg, ++. Eczematous reaction to patch tests: human dander, ++++; E.M.Z. eczema scales, ++++. Avoidance of human dander was followed by a great deal of improvement even during the cold winter months. Some lesions, however, persisted.

Case 3.—T.O.T., a boy, aged six months, had eczema of three months' duration on the face, upper and lower extremities and trunk. The family history of atopy was negative. Urticarial reactions to scratch tests: egg, +++. Eczematous reactions to patch tests: human dander, negative; E.M.Z. eczema scales, negative; his own dander, negative; his mother's wool coat, negative. The eczema continued without much change. He sucked both index fingers. These were eczematous. Other fingers which were not sucked appeared normal. Saliva gave a negative patch test.

Case 4.—D.H., a girl, aged nine months, had eczema on her cheeks and upper and lower extremities, of four months' duration. The family history of atopy was negative. Urticarial reactions to scratch tests: egg, +++. Eczematous reactions to patch tests: human dander, ++++; E.M.Z. eczema scales, negative. Her clinical course was very irregular and capricious. Several periods of great improvement were followed by exacerbations. She was placed in the hospital and, after four days without improvement in her condition, was given soy bean milk, cow's milk being withheld from her diet (skin tests to cow's milk were negative). In two days she was much improved. During the succeeding seven days, however, her eczema became greatly aggravated and was really more severe than at the time of admission. This exacerbation occurred while she was on a soy bean diet without cow's milk and without egg. (Eggs were withheld during the entire period of observation—before, during and after hospitalization). She was then put on a cow's milk formula, remained in the hospital four more days, and left with her eczema in practically the same condition as at the time of admission.

Case 5.—L.L.W., a girl, aged three months, had eczema on the face only, especially on her cheeks, of six weeks' duration. The family history of atopy was negative. Urticarial reactions to scratch tests: egg, ++. Eczematous reactions to patch tests: human dander and E.M.Z. eczema scales, both negative. The eczema persisted. Avoidance of human dander, as expected, was of no value in treatment.

Case 6.—M.A.D., a girl, aged three, had eczema in the cubital spaces and on her forearms and hands of twelve months' duration. The skin was lichenified as in the

adult type of the disease. Unlike most cases there was no seasonal variation in the lesions. Her mother had hay fever. Egg gave a + urticarial reaction to scratch test. Human dander gave a very slight reaction (±) to patch test. E.M.Z. eczema scales produced a + + + + eczematous reaction to patch test. Avoidance of human dander, as expected, was of no benefit.

Case 7.—P.O., a girl, aged three, had eczema of the cheeks and in cubital spaces of two years' duration, present in cold weather but absent in the summer. Her father had hay fever. Egg gave an urticarial reaction to scratch test (+ + +), and when eaten was followed immediately by generalized urticaria (but not by an exacerbation of eczema). Eczematous reactions to patch tests: human dander, + + +; E.M.Z. eczema scales, +. Avoidance of human dander was followed by disappearance of the lesions on the cheeks and improvement of those in the cubital spaces. Residual eczematous lesions persisted, however, in the cubital spaces until the summer season.

Case 8.—M.L.B., a girl, aged two, had eczema on the face of one year's duration, better in summer, worse in winter. Her mother had asthma. There were negative urticarial reactions to foods and inhalants. Human dander gave an eczematous reaction to patch test (+ +). Avoidance of human dander was followed by complete disappearance of the lesions in one month.

Case 9.—N.J.M., a girl, aged nine, had had eczema in the cubital spaces and on her arms, forearms and neck since infancy. In the past she had also had lesions on the scalp and in popliteal spaces. The lesions were much less extensive and less severe (sometimes disappearing entirely) in the summer. She also had hay fever and asthma, but there was no definite family history of atopy. Urticarial reactions to scratch test: ragweed pollen, + + + +; house dust, + + +; human dander, + + +. Eczematous reactions to patch test: human dander, (on normal skin) ±, (on scarified skin) + + +; ragweed pollen, (on normal and on scarified skin) negative; E.M.Z. eczema scales, (on normal skin) negative, (on scarified skin) +. Human dander rubbed on abdomen resulted in numerous itchy papules which persisted for a week. Avoidance of human dander was followed by remarkable improvement lasting many weeks during the winter season. In the cubital spaces and on the neck, however, definite eczematous lesions remained in spite of the best of care in avoiding dander.

Case 10.—D.H., a girl, aged thirteen, had eczema of the face, neck, upper chest and upper back in the area not covered by her dress. Her eczema began at two years of age and lasted to three years of age, recurred at six years of age and lasted to present time. Her father's sister had hay fever. Scratch tests gave urticarial reactions to ragweed and grass pollens and to human dander. Eczematous reactions to patch test on scarified skin: human dander, + + (the test was negative on normal skin); E.M.Z. eczema scales, negative. Human dander was rubbed on the same area on an arm once daily for five days. No lesions appeared. She pursued a very irregular clinical course with little, if any, improvement which could legitimately be attributed to avoidance of dander.

Case 11.—E.M.Z., a girl, aged thirteen, had had eczema over almost her entire body since six months of age. In the summer it improved remarkably and often left entirely, but recurred every fall and lasted all winter. One sister and one brother had atopic eczema. Urticarial reactions to scratch test: foods and inhalants, all negative. Eczematous reactions to patch test: human dander, (on normal skin) negative, (on scarified skin) + +; E.M.Z. eczema scales (her own), negative on

TABLE I. RESULTS OF DIMINISHED EXPOSURE TO HUMAN DANDER

No.	Age (Yrs.)	Sex	Duration of Eczema	Location of Lesions	Other Allergy in Patient	Family History of Allergy	Urticarial Reactions to Scratch Tests	Eczematous Reactions to Patch Tests With Human Dander		Clinical Course of Disease
								On Normal Skin	On Scarified Skin	
1	2	M	12 mos.	Face, cubital spaces, forearms	—	+	Ragweed pollen ++	++		No definite improvement
2	2	F	12 mos.	Face, hands, wrists, rt. forearm, pop. spaces	—	+	Egg ++	++++		Much improvement but some lesions remained
3	½	M	3 mos.	Face, upper and lower extremities and trunk	—	—	Egg +++	—	±	No improvement
4	¾	F	4 mos.	Face, upper and lower extremities and trunk	—	—	Egg +++	+++		No improvement attributable to dander avoidance either at home or in hospital
5	¼	F	6 wks.	Face only	—	—	Egg ++	—	—	No improvement
6	3	F	12 mos.	Cubital spaces, forearms, hand	—	+	Egg +	±	—	No improvement
7	3	F	2 yrs.	Cheeks, cubital spaces	—	+	Egg +++	+++		Definite improvement, residua lesions persisted
8	2	F	1 yr.	Face only	—	+	—	++		Cleared entirely in 4 wks.
9	9	F	8 yrs.	Upper extremities, neck, cubital spaces	+	—	Ragweed pollen ++++ House dust +++ Human dander +++	±	+++	Improvement but lesions persisted on neck and in cubital spaces
10	13	F	Age— 2 to 3 yrs. 6 to 13 yrs.	Face, neck, chest where not covered by dress	—	+	Ragweed pollen + Bluegrass pollen + Human dander +++	—	++	No definite improvement
11	13	F	12½ yrs.	Generalized	—	+	Human dander ±	—	+	No definite improvement
12	15	F	14 yrs.	Neck, cubital spaces, fingers	+	+	Ragweed pollen +++ Human dander ++	+	+++	No definite improvement
13	22	F	21 yrs.	Face, neck	+	+	Dog dander + Human dander ++	—	++	No improvement in 3 wks.
14	36	F	Many yrs.	Face, neck, right cubital space	+	—	Human dander +++	—	++	Great improvement in cubital space. Little improvement in face

both normal and scarified skin. (This patient's eczema scales—designated "E.M.Z. eczema scales"—were found to be the most potent in their capacity to produce eczematous reactions to patch test. On the patient herself, however, they produced no reaction). Her clinical course was modified very little, if indeed at all, by avoidance of human dander. In this case the hair was cut very short in order that the scalp might be washed more thoroughly.

Case 12.—A.W., a girl, aged fifteen, had had eczema on her neck, cubital spaces and fingers since infancy. She also had perennial hay fever, and the family history was positive for atopy. Urticarial reactions to scratch test: ragweed pollen, +++; human dander, ++. Eczematous reactions to patch test: (on normal skin) human dander, +; (on scarified skin) human dander, +++, and E.M.Z. eczema scales, negative. No definite improvement attributable to dander avoidance. She cooperated poorly.

Case 13.—Mrs. C.H., a woman, aged twenty-two, had had eczema on her face and neck since infancy, only during cold weather. It left in summer but recurred in the fall. She also had had definite vesicles on the right thenar eminence, which may have been an irrelevant condition. She had mild perennial hay fever. The family history was positive for atopy. Urticarial reactions to scratch test: dog dander, +; human dander, ++. Eczematous reactions to patch test: (on normal skin) human dander, negative; and E.M.Z. eczema scales, negative; (on scarified skin) human dander, ++, and E.M.Z. eczema scales, +++. She had been rid of eczema for many months when her husband returned from overseas. Five days later the eczema recurred on her face and neck. The husband had unusually large amount of dander on his scalp. The eczema persisted for three weeks and was present when she left the city. No further notes are available.

Case 14.—Mrs. J.A.M., a woman, aged thirty-six, had had eczema since early childhood. When first seen, the lesions were present on the face and on the neck down to the dress line, where a sharp margin separated the lesions on the neck from the normal skin covered by the dress. The left upper extremity was entirely free of lesions but the right cubital space and adjacent areas of the right arm and forearm were involved in a severe eczematous reaction. This woman had the habit of invariably sleeping on the right side with the right arm in contact with her forehead. The family history was negative for atopy. Urticarial reactions to scratch test: human dander, +++; foods and inhalants, negative. Eczematous reactions to patch test: (on normal skin) human dander, negative, and E.M.Z. eczema scales, negative; (on scarified skin) human dander, ++, and E. M.Z. eczema scales, negative. This woman was told to wear a long sleeve on the right arm day and night, to wear a short sleeve on the left arm and to sleep on the left side with the left arm in contact with the forehead. After twenty-seven days the right arm and forearm had almost entirely healed and the left arm and forearm had become eczematous, but not to the same extent as the right arm had been 27 days before—in fact, the left was involved only about 5 to 10 per cent as much as the right had been. Two months later both upper extremities had only traces of eczema, but the face and neck were only moderately improved.

RESULTS

Clinical evaluation of the results of treatment in this disease is admittedly hazardous. There are many factors, both known and unknown, which cannot be controlled in the home, and this statement is true also regarding hospital treatment. Periods of improvement lasting only a few

days to a week were considered to be of no significance but were regarded as being merely natural variations in the clinical course of the disease (having causes, of course, but causes which could usually not be identified).

Three of the fourteen patients were not allergic to human dander. As expected, none of these benefited by dander avoidance (Table I). Of the remaining eleven cases, six exhibited no definite lasting improvement; four showed definite improvement, and in one case the lesions cleared up entirely. In the four cases showing improvement but not complete disappearance of the eczema, the most persistent remaining lesions, as a rule, were those in the flexure of the cubital space.

DISCUSSION

From the results of these observations, together with evidence presented in previous publications,[2-6] it appears that in the disease, atopic eczema, human dander is responsible for part of the lesions in some cases and perhaps even for all the lesions in a small percentage of cases. It appears to be very improbable, however, that *surface contact* with human dander is responsible for (1) the persistent lesions in the four cases which showed definite improvement, (2) the major portion of the lesions in the six unimproved patients who were found to be allergic to human dander, and (3) the lesions in the three patients not allergic to human dander. While human dander is capable of causing the disease, and does cause the disease, and is, I believe, the most important *known* allergenic excitant of the disease, it is very probably not the most important *existing* allergenic excitant of the disease. The evidence, as it stands, indicates that there are one or more unidentified excitants. These should be investigated and identified if possible.

II. CUTANEOUS REACTIONS TO ECZEMA SCALES

In connection with the causative factors involved in the pathogenesis of this disease, the question arises, why (in any particular case and in cases in general) do the lesions involve the skin areas which they do involve rather than some other skin areas? The following theoretical possibilities were considered: (1) that involved skin areas contain a higher concentration of allergen than uninvolved areas, (2) that in involved areas for some unknown reason (flexion and extension? thinness of epidermis? perspiration? other mechanical trauma?) the allergen (not necessarily present in higher concentration) is able to penetrate more readily to the reactive tissue, (3) that involved areas are specifically more highly sensitized than uninvolved areas, and (4) that nonspecific, nonallergic factors determine the location of the lesions (related to item No. 2.).

Previous observations[6] indicated that involved skin areas are not specifically more highly sensitized than uninvolved areas. Attention, therefore, was directed toward other possibilities, especially toward that of the pos-

TABLE II. PATCH TESTS WITH ECZEMA SCALES AND HUMAN DANDER

A. ON PATIENTS WITH ATOPIC ECZEMA

Case No.	Age (Yrs.)	Patch on Normal Skin			Patch on Scarified Skin		
		Human Dander	E.M.Z. Scales	Petrolatum	Human Dander	E.M.Z. Scales	Petrolatum
1	½	++	—	—			
2	2	+	+	—			
3	3	+++	±	—			
4	1	++	—	—			
5	2	++	++	—			
6	2	++	++	—			
7	½	—	—	—			
8	2	++	—	—			
9	¾	+++	—	—			
10	2	++	++	—			
11	¼	—	—	—			
12	3	±	+++	—			
13	3	+	++	—			
14	2	+++	++++	—			
15	1	++	—	—			
16	2	+++	++	—			
17	17	—	—	—	+	—	—
18	12	—	—	—	++	—	—
19	13	—	—	—	++	—	—
20	11	—	—	—	++	—	—
21	9	—	—	—	++	+	—
22	36	—	—	—	++	+	—
23	22	—	—	—	++	+	—
24	26	—	—	—	+	—	—

B. ON NONECZEMATOUS CONTROLS

1	2	±	±	—			
2	1	±	—	—			
3	1	—	—	—			
4	1	—	—	—			
5	2	—	—	—			
6	3	—	—	—			
7	32	—	—	—	—	—	—
8	21	—	—	—	—	—	—
9	41	—	—	—	—	—	—
10	15	—	—	—	—	—	—
11	18	—	—	—	—	—	—
12	20	—	—	—	±	+	—

sible presence of allergen in the lesions. This was done even though previous attempts to discover detectable quantities of human dander *allergen* in the lesions (of atopic eczema) had met with failure.[6] A search was being made for allergens other than the human dander allergen. Several patients were tested with their own eczema scales. The tests were made on uninvolved skin areas by scratch, patch on normal skin and patching on scarified skin.[5] These tests were all negative. Tests were then made on one patient with eczema scales from other patients. Approximately 200 tests were performed with eighteen different scale specimens. While most of these tests were negative, it was found that the eczema scales from certain patients possess the property of producing eczematous reactions to patch tests (on normal unscratched skin) on certain other patients with atopic eczema. Furthermore, eczema scales from different patients possess this property in varying degree. The scales of one patient, E.M.Z., a thirteen-year-old child with severe, almost generalized, atopic (?) eczema, possessed this property to somewhat greater degree than the others. Table II shows the results of patch tests with E.M.Z.'s eczema scales.

The scales were mixed with sufficient petrolatum to make a thick paste and applied as a patch test with adhesive tape in the usual manner. The patches were allowed to remain in position two days. Readings were made several hours to one day after removal of the patches. The reactions consisted of papules, papulo-vesicles, redness, slight swelling and later slight crust formation and desquamation. The mild reactions lasted three or four days. In one case they remained distinctly visible for three weeks and in another case for four weeks. The stronger reactions were typical areas of eczema, indistinguishable from other naturally occurring lesions on the patient. Twenty-four eczematous patients were tested. Sixteen were less than four years of age. Eight of these gave positive reactions to patch test on normal skin. Eight were more than nine years of age. Three of these gave positive reactions to patch on scratch test. Of twelve non-eczematous controls, ten gave negative reactions, one a questionable reaction and one a slightly positive reaction (Table II).

DISCUSSION

The lesions of certain cases of atopic eczema were found to possess eczematogenous properties and evidently contain an eczematogenous agent. This agent is not a primary irritant, as shown by negative reactions to patch tests on noneczematous persons; it is probably an allergen. Its chemical nature and biologic origin are undetermined. A study of Table II shows that the reactions to E.M.Z. eczema scales do not parallel those to human dander. (Note especially Cases 9 and 12.) Hence, the allergen of these scales is not identical with the human dander allergen.

The etiological significance of these reactions is unknown. The implication, however, is that the lesions themselves contain an etiologic agent of the disease. This agent may possibly have its origin in some micro-organism or it may arise in the epidermis itself as the result of some antigenic modification of cell substance as the cells are pushed outward from the *stratum germanitivum* toward the *stratum corneum*.[1] In this connection several questions arise, among them being the following: Why did E.M.Z. give negative reactions to her own eczema scales while certain other patients gave positive reactions to these scales? A possible answer to this question may be that E.M.Z. is relatively less sensitive, and certain other patients relatively more sensitive, to an allergen present in high concentration in E.M.Z. eczema scales and present in lower concentration in eczema scales of certain other patients. Questions of infection arise. Tests must be made with sterilized scales. Needless to say, much work remains to be done.

SUMMARY

1. Eleven of fourteen patients with atopic eczema were found to be allergic to human dander. Diminished contact with human dander was followed by (a) complete disappearance of the lesions in one case, (b) definite improvement but not complete disappearance of the lesions in four cases,

(c) no definite improvement in six cases allergic to human dander nor in three cases not allergic to human dander.

2. Scales of the lesions of certain patients with atopic eczema were found to possess the property of producing eczematous reactions to patch test on other patients with the disease. Eczema scales from different patients possessed this property in varying degree.

Patch tests performed on twenty-four patients with the most reactive scale specimen resulted as follows: (a) on sixteen children less than four years of age, tested on normal skin, eight were positive and eight negative; (b) on eight persons, nine to thirty-six years of age, tested on scarified skin, three were positive and five negative. Controls on ten noneczematous persons resulted in one slightly positive and one questionable reaction.

Patch tests performed simultaneously with human dander on the same twenty-four patients (and on the controls) indicate that the eczematogenous agents of human dander and of atopic eczema scales are not identical.

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SENSITIZATION TO PETROLATUM IN OINTMENT BASES

(Continued from Page 583)

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RAGWEED DERMATITIS

Therapy by the Oral Route

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RAGWEED is but one of more than a hundred plants which may cause dermatitis of the allergic contact type. While it may present the picture of acute dermatitis seen after exposure to poison ivy, oak, or sumac, the usual clinical picture is that of a chronic dermatitis.

Because of the fact that many plants cause dermatitis, Sulzberger[1] feels that "it is almost certain that dermatologists as well as allergists must from time to time see and fail to recognize contact dermatitis caused by weeds."

The eruption is usually distributed on the exposed surfaces of the body, such as the face, neck, forearms, hands, legs and feet, and may become generalized.[2] The condition is not hereditary, and those who acquire the dermatitis from the ragweed plant do not suffer from hay fever or asthma. There is no naturally acquired immunity, the tendency being to suffer more severely on each subsequent occasion.

The first reported cases appeared in 1918. In 1928 it was established that the exciting cause of the dermatitis was the oleoresin of the ragweed plant and pollen. At this time it was found that the patch test was the only method of confirming the diagnosis.

The important factor in the diagnosis is its seasonal incidence and recurrence, the symptoms appearing in August and ending with frost, corresponding with the period of pollenation of ragweed. However, symptoms may appear as early as May, when the ragweed plant begins to grow, and may continue well up until November, as the ragweed plant maintains its vitality until that time. Contact with the withering plant is possible until it is rotted by the snow. Ragweed seed in the ground may cause symptoms all winter if handled.

Symptoms may be present at other times, such as while hunting, weeding, or handling hay or grain. The symptoms may also be continued by exposure to pyrethrum, turpentine, vegetable oils, and industrial sensitizers.

CASE HISTORIES

Case 1.—L. W., aged forty. The dermatitis first appeared in August, 1940, while the patient worked as a gardener. The eruption was generalized, as far as he can remember, and lasted all year. He has had similar episodes each year since, beginning about the same time of the year, in May, and lasting until after the first of the year. He is usually free from symptoms from January to May.

There is no history of personal or familial allergy. Turpentine fumes and rainy weather cause exacerbations.

Read at the third annual meeting of the American College of Allergists, Atlantic City, N. J., June 6-8, 1947, by Dr. Francis, chief of the allergy clinic of the Rochester General and Highland Hospitals.

Dr. Slater is associate director of the Eastman Kodak Company, with which Dr. Norris and Dr. Francis are also affiliated.

The patch test with ragweed oil was markedly positive. It was removed two hours after application because of intense itching. This patient took ragweed oleoresin orally in 1946. His skin was normal that year.

Case 2.—L. B., aged fifty-three. The patient was well until late summer of 1938 when he developed eczema of the hands, scrotum, legs, and face. He was seen by a dermatologist, who found him very sensitive to ragweed, goldenrod, and metallic silver. The condition cleared in the early winter, to recur in October, 1939, clearing considerably in mid-November, but not to a degree permitting normal activity. It became much worse in October, 1940, and at this time, because of its persistence throughout the preceding year, it was thought that the patient might be sensitive to some of the chemicals with which he was working. There was a positive patch test to one of these. On November 1, 1943, there was a very severe flare-up of dermatitis, following a hunting trip and a garden clean-up, when tomato vines were handled. In January, 1944, he reported that merely his presence in the workroom caused his face, neck and arms to burn, smart, and itch. He had been taking oral ragweed antigen for some months, but he did not wish to continue. An acute flare-up frequently occurred following incorrect dosage. His work was shifted to another area where the material used involved only dry gelatine, but the eruption persisted. The occupation was changed to water purity control where the only possible exposure might be to infinitesimal quantities of chlorine. The most acute exacerbation occurred, however, in September, 1945. The patient went to the mountains, where he improved very promptly, and was nearly well when he returned home a month later.

The condition flared up promptly again, so that hospitalization was necessary. He returned to work on December 10, 1945, still with considerable chronic eczema. This persisted, especially on the legs, during the following winter and spring, becoming worse in July. He spent August, September and October in the Adirondacks, returning to work November 4, 1946. He has been very much better since that time, even though working in an area where he had previously had trouble. The face and trunk are nearly clear, the only area remaining active being on the legs. It is proposed that he return to the mountains during the ragweed pollen season.

RAGWEED DERMATITIS ORAL DESENSITIZATION

I. Etiology.
   A. Predisposing causes.
      1. Older males (twenty-eight to seventy-four).
      2. Farmers.
      3. Season: July to frost.
      4. Not hereditary.
      5. Long exposure.
      6. Hunting.
      7. Weeding.
      8. Handling hay and grains.
   B. Exciting cause.
      1. Ragweed—ether extract of pollen or leaves (if patient is sensitive to one weed, he is usually sensitive to all of its botanically related members).

II. Symptomatology.
   A. Early symptoms consist of red, tender, edematous lesions of eyelids and neck, spreading to other parts of the body by hands, clothing, and the application of greases.
   B. Aggravated by wind—better with rain.
   C. Average eruption is three months—July to frost.

III. Pathology.
  A. Subacute inflammatory reaction of type seen in chronic eczema or dermatitis.
IV. Diagnosis.
  A. Positive ragweed test confirms diagnosis.
  B. Negative test to:
    1. Pyrethrum
    2. Turpentine
    3. Potassium (arsenite 1 per cent)
    4. Corrosive mercury chloride (1 per cent)
V. Treatment.
  A. Wet dressings, lead acetate and Burow's solution, soothing baths and drying lotions.
  B. Change of environment.
  C. Desensitization, oral.
    1. Total amount required: at least 2 c.c. of ether extracted plant oleoresin.
    2. Administration: ingestion of 30 c.c. each of 1:100, 1:50, and 1:25 dilution in corn oil (provides approximately 2 c.c. of oleoresin extract).
    3. Time: two to eight months, depending on "tolerance" of patient.

Dilution	*Amount*	*Time*
1:100	1 drop	Daily—7 days
1:100	2 drops	Daily—7 days
1:100	Increase to tolerance until dilution is exhausted.	Daily
1:50	One-half the number of drops of 1:100 dilution increased to tolerance.	Daily
1:25	One-half the number of drops of 1:50 dilution increased to tolerance.	Daily

    4. Intolerance symptoms: pruritus ani, exacerbation of dermatitis.

DISCUSSION

These cases are of interest because they show the importance of recognizing ragweed dermatitis when it occurs in industry, since this type of dermatitis is not usually compensable. In the first case (L. W.), the seasonal incidence and recurrence of the dermatitis corresponds with growth and pollenation of ragweed, and the diagnosis is substantiated by a positive patch test to the oleoresin of ragweed. In the second case (L. B.), it appears that ragweed is the primary cause of the dermatitis, with continuation of symptoms best explained by other factors, some of which may be related by exposure to industrial sensitizers.

TREATMENT

At present, the best advice to give a patient who is afflicted with ragweed dermatitis is to go to a place where ragweed does not grow. If this is not possible, the treatment of choice is by oral desensitization, using the ragweed oleoresin in corn oil. According to Rudolf Baer, this may be a safe and effective method of desensitization for ragweed, and it has also been shown to be an effective method in some cases of poison ivy dermatitis. However, one must always be on the alert for intolerance of the ragweed oleoresin, which may produce an acute exacerbation of all the symptoms.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

POSSIBLE DANGERS IN MILD SHOCK THERAPY

The administration of pollen extract is, in general, a procedure which is not attended with any acute danger or repeated injury to the patient. However, in the experience of the editor, many allergists, following a certain school of thought in regard to therapy, increase the dose to just below the level of shock. Indeed, in certain clinics in this country reports of experimentally induced "mild" anaphylactic shock in patients undergoing therapy is reported with little thought of damage to the patient.

Recent experiments by Castberg and Schwartz* should lead those of us who are responsible for the welfare of the allergic patient to pause and take stock in the laxity of the recommendations often advised for allergic therapy. Castberg and Schwartz show that in five young hay-fever patients, following a shocking dose of pollen extracts, there were important changes in the electrocardiograph. In all cases, changes typical for anoxemia of the myocardium were found.

Although there was no evidence to suggest any specific allergic reaction in the heart and although the authors believe that changes depended upon decreased ventilation of the lungs, our attitudes in this case must be specifically connected with the welfare of the patient. Just what, for example, is the effect of overdosage over prolonged periods, for many years? Do doses producing subclinical shock in the tissues lead to chronic changes due to therapy? In view of the fact that this question cannot be answered, it appears desirable at present, to cautiously avoid shocking doses of allergens or doses of allergens beneath the shocking level in the therapy of hay fever and asthma.

EXPERIMENTAL TUBERCULIN SENSITIVITY

It has been known for a number of years that the immunological specificity of the tuberculin reaction is associated with a protein of M. tuberculosis, which has been isolated and studied in considerable detail. Such tuberculoproteins have proven in large scale tests to be proper reagents for tuberculin testing "PPD" of Seibert. Tuberculoproteins are true antigens. Animals injected with it form antibodies which give typical test tube reactions, and animals can be anaphylactically sensitized, but the delayed local and systemic reactions which characterize tuberculous infection could not be experimentally obtained. In the latest issue

*Acta Medica Scandinavica, Vol. 126, 1947, page 459.

of *The Journal of Infectious Diseases* (82:267, 1948), S. Raffel presents in detail the evidence which shows that delayed sensitization of the tuberculin type can be obtained in the guinea pig, if tuberculoprotein is given in admixture with the wax of the tubercle bacillus. By further fractionation of the wax, the activity was found to be associated with esters of hydroxy fatty acids with carbohydrates and higher alcohols, which have first been studied by Anderson. (This fraction also contains the "mycolic acid" which causes the acid-fastness of tubercle bacilli.) Both local and systemic reactions of the delayed type were produced in the guinea pig by the mixture of protein and wax. The characteristic toxic reaction of the explanted bone marrow of sensitized guinea pigs was also obtained with these mixtures. It appears that the wax modifies ("directs," as Raffel puts it) the antigenic effect of the protein. The mechanism of this "directing" activity is unknown, except that in a negative way it can be stated that it is unlike the adjuvant action of paraffin oil and related substances.

Beyond the high factual interest of these observations, their impact on our conceptions concerning allergy of the delayed or "infectious" type is bound to be considerable. Raffel mentions unpublished data which showed a similar modifying influence of the wax on unrelated antigens, e.g., egg albumin. A new rationale for experimental approach to problems of supersensitivity seems thus to be opened.

FOOD SENSITIVITY IN ASTHMATIC CHILDREN

Hill[1] states: "That food can cause asthma in children is a fact beyond dispute. The frequency of this sensitivity, as well as its relative importance to recurrent respiratory infection, sensitization to pollens and other environmental allergens, is an entirely different question, concerning which there is considerable difference of opinion."

This thought-provoking paper brings into sharp focus the necessity for careful interpretation of positive food tests in asthmatic children, for Hill finds that only about 20 per cent of the positive tests are of clinical significance. It emphasizes anew the need for complete evaluation of all factors involved in skin testing. One must not conclude that food sensitivities are of no significance, however, but attention must be paid to the fact that sensitization to pollens and other environmental allergens are perhaps more frequently of greater significance than is generally thought.

Hill deplores the use of elimination diets, and this warning is well given, for children subjected to restrictions may suffer serious nutritional difficulties. He states: "Positive tests to foods have the same significance as positive tuberculin, trichophytin or brucellergen tests, namely—that at some time the organism has been exposed to antigenic material and an immunological reaction, which may or may not have anything

to do with the clinical condition under consideration, has occurred." In line with this thought, Ratner and Untracht[2] have shown that children, at one time highly sensitive to egg white both clinically and by skin test, may retain a residual skin reactivity years after their clinical sensitivity has worn off.

Hill's paper clearly demonstrates the importance of the careful evaluation of skin tests. It should make us conscious of their limitations, but it should not lead us to disparage the skin test, nor to curtail the number of tests performed. Rather, the relative importance of each positive reaction should be carefully appraised in the light of all accumulated findings in the individual case.

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RAGWEED DERMATITIS

(Continued from Page 596)

SUMMARY

1. Two cases of ragweed dermatitis were presented.
2. Both were treated by the oral method, using the ragweed oleoresin in corn oil.
3. One patient was symptom-free for a year. The other patient had to discontinue treatment because of intolerance.

We gratefully acknowledge the photographs by Miss Merlynn Cook, A. B., which were presented originally with this paper.

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Progress in Allergy

MISCELLANEOUS ALLERGY

A Review of Recent Literature

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In reviewing allergy literature during the past year, the impression has again been gained that much effort is being utilized in the search for newer methods and approaches to measures that will insure more exact diagnostic possibilities and more definite expressions of benefit. The review of last year[49] was arranged in a fashion which grouped the various phases of allergy together and excluded those subjects adequately covered by other writers. This seemed to be the most satisfactory manner for a presentation of a review of this type, particularly when there are so many specific instances which could easily be a part of the other reviews dealing with sectional material. Again, the reviewed material is being presented according to the following outline: (1) General, (2) Respiratory, (3) Dermatological, (4) Gastrointestinal, (5) Headache, (6) Infection, (7) Histamine and Antihistaminic Preparations.

GENERAL

More attention during the past year has been paid to the close association between the allergic picture and the precipitation of these symptoms by emotional disturbances and responses. Abramson[1] points out the lack of communication between two journals, one devoted to the study of allergy and the other devoted to the subject of psychosomatic medicine. During a period of seven years, the latter publication presented twenty papers relating specifically to the emotional problems of the allergic state, while the former journal had only one brief report on the same subject. He feels that too much emphasis has been placed on the histamine theory in an effort to explain the allergic phenomena. Abramson further states that several publications have dealt chiefly with this theory but only a few have been directed toward the basic explanation of "why" the histamine theory does not answer all the questions involved. He presents several interesting cases in which the diagnosis of allergy was very definite, but in whom the mechanism of their symptoms was specifically aggravated or initiated by psychodynamic forces. Patients are also described in whom the allergic symptoms were not proven to be immunologically allergic. He calls for two steps that seem necessary for fundamental advance in the specialty of allergy.

Editorials and contributions of an allergic nature should be sought and published by the journals dealing with psychosomatic material, and contributions designed to emphasize the role of emotional factors in the allergic patients should be encouraged by the editorial staffs of the allergy journals. This author also points out that the early recognition of anger and hostility as influencing factors upon the allergic paroxysm had its origin in the time of Hippocrates.[2]

Mitchell et al[67] have decided that a basic re-evaluation must be made of the generally accepted allergic etiology in those groups of patients discussed in their article. In the "reacting" group of patients, the incidence was noted to be about equally divided between the sexes. In the "non-reacting" group, there was a noticeable predominance of females, with the majority of patients being in the third, fourth and fifth decades. The authors could not explain this variation on a basis of

allergy and the speculation is made that the difference lies in the personality factors and adjustments that are most common within the home circle. The realization that confusion, fear, hostility, family or office troubles and the like are of marked importance has led them to the more satisfactory diagnostic and therapeutic approach resulting in their ability to help patients in whom they had previously experienced failure. Of 100 cases of perennial asthma, 21 per cent were considered psychologically maladjusted in view of the expressions of confusion, guilt, fear and hostility made in the initial history interview. Metzger[65] considers neurotic factors to be frequently of considerable and primary importance in patients complaining of allergic symptoms. The allergist, and the psychiatrist as well, must be aware of the possible aggravation of allergic symptoms and emotional disturbances by either specific sensitization or fears and fixed ideas.

Chemical factors in asthma have been very adequately reviewed by Wiswell and Rackemann.[112] They state that though vitamin deficiencies are not the likely causative factors of asthma in any instance, such deficiencies may aggravate an asthmatic state already present. Other factors—blood sugar, calcium, phosphorus and magnesium—remain unchanged usually in the asthmatic individual and therefore no relationship can be demonstrated. The acid-base balance is of importance because of the excessive CO_2 which may result from insufficient pulmonary ventilation, and thus cause increased dyspnea. Though there is no indication that electrolyte and water balance changes are directly effective in asthma production, a marked shift may aggravate or improve the asthmatic complaints. Coca[18] made a study of the antiallergic effect of sympathectomy and sympathetic ganglion block. He has demonstrated the weakness of histamine injections as contrasted with the selectivity of sympathectomy. Cases are presented in evidence and the effect of ganglion block may be of sufficient duration to forecast the antiallergic effect of sympathectomy. Kline[55] considers the tissue changes in allergy under five headings: functional, inflammatory, proliferative, degenerative, and necrotic. The functional changes bear no detectable morphologic alteration of cells. Allergic reactions are stated to be characterized by rapid onset, violent course and slow regression. This certainly is characteristic of the patient with severe seasonal hay fever! This author considers the tissue changes in allergy to reflect the severity of the signs and symptoms of the reactions, even though some animals in anaphylactic shock fail to reveal any appreciable morphologic change of sensitized smooth muscle. Various methods of testing for drug sensitivity have been outlined and discussed by Hansen-Pruss and Leeper.[50] Skin testing, not always accurate in this determination, offers several possibilities. Passive transfer testing by injection of serum supposed to contain the antibody is followed by oral administration of the drug. The drug then would be subject to the processes of digestive metabolism and might stand a good chance of producing a positive reaction at the site of serum injection.

Recurrent parotid swelling occurring shortly before the onset of asthmatic attacks has been described by Waldbott and Shea.[113] The elimination of offending foods produced relief from both parotitis and asthma. The fact that the parotitis may occur for many years prior to the onset of asthma should influence all practitioners to the prediction of asthma with the presence of undetermined parotitis as of allergic origin.

Active allergy as a common cause of growth failure has been described and presented by Cohen and Abram.[20] They were able to follow 150 allergic children in private practice and determine that the frequency of allergy is more marked in the slender, constitutionally adapted male child. They discuss a grid method whereby the growth failure of these allergic children may be followed and frequently be detected. Immunity based on antibody formation has been presented

as a specific type of resistance in that the lymphocyte has a definite relationship to immune globulin production. White[109] feels that the adrenal cortex is one of the most important hormones involved in immunity production. Editorial policy has outlined the difference between cumulative and non-cumulative dosage plans.[83] The former involves the administration of small doses repeated at such intervals as to cause a final tissue concentration sufficient to produce the therapeutic effect desired. The non-cumulative method requires the administration of a single dosage effective in itself after the complete elimination of the previous amount. Some drugs require many days for the cumulation of effectiveness, while others may have the so-called side effects presented by single dosage administration. Proetz was unable to find any association between the severity of symptoms of vasomotor rhinitis and the basal metabolic rate.[79] Thirty-seven of eighty-four patients were improved on thyroid therapy, though thirty-four were known to have definite hypothyroidism.

Randolph[82] has continued his very interesting studies of the blood in allergic states. The original work of leukocyte changes following the trial feeding of foods was extensively studied by Vaughan. This author has done well in continuing the impression of eosinophilic changes and their importance. He has shown that the postingestion eosinopenia which occurs simultaneously with the production of allergic symptoms is identical with the response of the blood and the clinical picture observed in drug allergy. Many patients will develop a delayed eosinophilia which is noted to be in evidence as the clinical picture is found to be subsiding. This response is not commonly noted during the first hour after the ingestion of food or drug. Single or repeated feedings in normal persons were found to be not followed by a constant variation in the eosinophile level.

Eighty-six per cent of over 1,500 patients showed negative reactions to intradermal skin tests with iodopyracet. Alyea and Haines[5] found that, of these 14 per cent positive reactors, thirty-four of them experienced the general type of reaction. Their findings have shown that the patient with a positive family history, a personal history and positive skin test reactions to diodrast is most likely to have a general reaction to the drug. The warning is given, however, that the physician using the drug should be on guard for the unusual patient who will present systemic reaction symptoms with no previous indication of allergy in self or family. The ability of the adrenalectomized rabbit to produce antibodies has been the source of study for Murphy and Strum.[70] Such production seems to result from a hypertrophy of the lymphoid tissue and prevention of the adrenal cortical hormones does not reduce this indication. In fact, there was no difference between the titers of hormone-treated and hormone-untreated operated rabbits.

The standardization of both pollen and dust extracts has been the source of discussion and experimentation over a period of the past several years. There have been many interesting and erudite articles published on the subject and each seems to include the plea to all allergists for support in the contention that extracts must be placed upon an acceptable standard before satisfaction can be reached. Extract standardization has been the particular interest of the American College of Allergists. The Standardization Committee of the College has published their report upon the various methods used for the standardizing of allergenic extracts.[87] Evidence is thoroughly presented to show that there is no relationship between the skin reactivity and the total nitrogen present in an extract. Nitrogen is considered to be a poor method of standard in view of the variation in the molecular size of the various antigens—in this instance, dust. Extracts whose antigens are of the same molecular size (and when adjustment is made for the phosphotungstic acid precipitate nitrogen—different from total nitrogen—so that this factor was constant) were productive of somewhat more constant degree of skin reactivity with less over-all error. A successful standardization of dust extract, therefore, can only be reached by a combination of chemical and biological methods. The ideal

extract gives a positive reaction on a clinically known sensitive patient, and a negative reaction on the normal control individual. Rimington and his associates[83,84,85] feel that the antigen in the house dust extracts used by them was only a very small part of the total material. They preferred heated fractions of the extracts to those prepared by Seitz filtration because of the stronger intracutaneous reaction produced by the former. They felt that this might be due to the lack of filtrable viruses destroyed by heating. They have also worked with mold extracts and found that in their patients no positive reactions were determined for mold extracts in association with negative dust reactions in that patient. Wodehouse[115] discusses the various methods of pollen extract standardization and describes each in some detail. By comparing two apparently similar grass pollen extracts, this author has found a difference in their reactive potency by neutralization of reagin at local passive transfer sites. The extent of the neutralization has been revealed by retesting these sites with standard pollen extracts. This reviewer is of the opinion that the standardization of allergenic extracts upon a basis acceptable and usable by practicing allergists is the outstanding challenge to the specialty today.

RESPIRATORY

It is often found that the drug or method of therapy used to obtain relief in one patient will cause alarming and untoward symptoms in the next. Greenblatt[45] has reported the use of Privine hydrochloride in the treatment of rhinitis in a patient two months of age. About thirty minutes after the installation of a few drops of the 0.05 per cent strength of the solution, the patient was found to be lethargic, and markedly stuporous. The symptom-picture was noted for about three hours, after which a very gradual and uneventful return to normal was experienced. This same author has reported to this reviewer[46] two similar instances occurring with the same drug, though not in the same method of application. Hainesworth[48] cites his case in which the patient noted almost immediate symptoms following the swallowing of about 3 to 4 c.c. of 0.1 per cent Privine. Unconsciousness eventually was quite profound. After a rather stormy period of hours, a return to normal was reported. Sensitivity to powdered sulfonamide compounds has been reported by Ballenger[9] when he describes the use of this type of medication application in 1,500 patients. Of these patients, to whom over 6,000 treatments were given, only seven experienced some type of evident allergic reaction to the drugs. Good results were noted in the abatement of the infectious processes and a definite lessening in the percentage of complications.

Over the period of the past few years, there has been a rapidly spreading interest shown in the use of radium application to the nasopharynx in the treatment of both chronic infectious and allergic states. The radium can be purchased outright for use or can be rented by the practitioner for use in his limited number of patients. Either method of obtaining the material is somewhat expensive, but results seem to indicate the justice of such procedure. Findlay[39] treated forty cases of nasal polyposis over a period of seven years. Insertion of the radium applicator followed a submucous resection and an exposure of the ethmoid labyrinth. His results showed that only four recurrences were experienced and there were no complications of any consequence. That irradiation of the nasopharynx is the treatment of choice for infectious or allergic conditions is expressed as the opinion of Crow.[25] A recurrence of lymphoid tissue following the removal of tonsils and adenoids in children is often given as the basic causative factor for the onset of aggravation of a bronchial asthmatic state. Radon or radium application has been successful in the control of this complicating or etiologic condition. Stansbury[101] in an unpublished series of similar cases has been quite enthusiastic about the results and the absence of complications with the use of the radium applicator. The technique of administration has been described by various authors and the reader is

referred to the various articles dealing with the use of the applicator. That surgical removal of adenoid tissue often is not adequate has been the basis of a report by Proctor.[78] In the process of repair following the surgical procedures, lymphoid tissue is present in the stroma of the mucous membrane serving as a replacement. As a result of infection or allergy, or a combination of the two, this lymphoid tissue is seen to grow rapidly and in good proliferation with an aggravation of an established bronchial asthma or an addition to an already or continuing nasal symptom-complex. This paper reports good results in 400 patients who received 1,100 radon treatments as adjunctives to the usual nose and throat measures. It has long been recognized that the simple removal of tonsils and adenoids will not benefit the average allergic patient, either nasal or asthmatic. Sixteen of thirty-four children reported by Ward et al[107] had had surgical removal of the tonsils and adenoids without lasting benefit. With recurring infections, severe asthma was noted regardless of the removal of exciting extrinsic causes. Complete disappearance of lymphoid tissue from the nasopharynx was seen in twenty-three of the thirty-four cases following the use of radon application on four occasions spaced at monthly intervals. Associated results showed that fifteen of these patients were completely relieved while eight of the twenty-three had a marked diminution in the frequency and severity of their attacks. Fuchs and Almour,[42] on the other hand, traced specific instances of deafness to the ingestion of fish, tomato, tobacco and powders. They propound that since epinephrine 1-1,000 subcutaneously was of benefit in the relief of the acute deafness, the basic pathology must have been a hydrops of the perilymphatic space causing impairment of auditory function by exerting pressure on Corti's organ.

Though the subject of seasonal hay fever is sufficiently large in practice and in literature to comprise a review in itself, it is felt that there may be instances wherein the nature of the material would justify its inclusion in this miscellaneous review. Certainly this is true of the mold studies that have made good progress in recent years. Mitchell et al[68] report the symptom of vulvo-vaginitis pruritus occurring as a major part of ragweed sensitivity in eight patients. Their patients were all children and responded exceedingly well to hyposensitization measures. The eight cases are presented in brief form and they give the impression that though this complex is relatively rare, seasonal vulvar itching is rather common in particular groups. The age of onset was under five in seven of twenty-four hay fever cases and between five and ten years of age in only one of fifty-five cases. They predict that the condition will probably not be encountered beyond adolescence. Each patient has his own individual level of pollen tolerance, whether it be in the nature of symptom production by inhalation or injection in therapy. Rackemann[80] discusses the work of previous investigators and presents several cases to show that good results can be obtained with a small series of extract dosages if the correlation is made between the amount per injection and the level of tolerance for that particular patient. It is always easier to obtain a better, more satisfactory, result in the treatment of hay fever in the second or the third year of therapy than in the first. Rackemann feels that this is due to the study of the patient's response to various dosages in previous years, which should always be used as a guide in the management of the seasonal hay fever in subsequent years. In this way, the level of "absolute tolerance" can be determined, and as long as the pollen dosage remains beneath that reactive level, no general reactions will be experienced from therapy. It should be emphasized, however, that that level may vary from patient to patient, and in the same patient from year to year. It has been this reviewer's thought that this reactive level may vary in the individual patient in the same year from time to time, and that this variation may be due to the amount of exposure or the rate at which the pollen extract is being supplied to him in therapy. It is

brought out that there is a discrepancy between skin test reaction and clinical sensitiveness and that there is a "constitutional" factor in hay fever which is quite apart from local cellular antibody. It is admitted that better results should be gained by experience with the same patient in successive years of therapy, but some determination must be made for that original year. It has been noted by this reviewer that the patient who has a poor result his first year of treatment is the reluctant patient in subsequent years, and usually falls back on non-specific measures for anticipated relief. Skin test reactivity or skin titration with various dilutions of pollen extract seems a more reliable method of dosage determination that first year at least, than does the guess and hope system. Rooks[88] has reported an all-glass cylinder to which is fitted a top and bottom of plate glass. The precipitating electrode is of platinum wire. The collecting electrode is a Petri dish through the center of which is inserted a copper rivet. The medium is poured to a sufficient depth to cover this rivet. He has found a very marked increase in the sampling efficiency by electrostatic precipitation as compared with impingement of the fungus spores. In a series of collected articles,[32,69,76,98] Prince and his co-workers have reported on their recent investigations with mold extract preparation and studies. Twenty-nine Alternaria-sensitive patients were tested by scratch and intracutaneous methods with extracts of frozen, unwashed, lyophilized pellicles of A. tenius and Aspergillus niger. Extracts prepared from washed pellicles were compared. No significant difference in skin reactivity could be determined in the Alternaria extracts. Patients clinically sensitive to Aspergillus niger were somewhat difficult to select, so the majority of comparative testing was done with the Alternaria-sensitive patients and extracts. The skin reactive fraction of the Alternaria extract tended to remain within the cellophane bag used in dialysis. It was suggested that the enzyme activity of the mold preparations altered the permeability of the cellophane to interfere with dialysis. Dutton found that treatment with mold extracts gave exactly the same results as the use of pollen extracts in the pollen-sensitive patient. Constitutional reactions were obtained with mold extracts in higher dosages and some patients experienced accentuation of their asthmatic symptoms while under therapy with comparatively high dosages. Morrow points out the "top ten" group of genera for all collecting stations to be Alternaria, Hormodendrum, Penicillium, Aspergillus, Pullularia, Torula fusarium, Trichoderma, sterile pale species and sterile dark species. She also reported that each station had a consistent "big six" which varied from station to station but were still listed in those mentioned above. The "top ten" should cover most of the testing for most of the men interested in allergy. Sellers feels that desensitization therapy with mold extracts is definitely worth while.

DERMATOLOGICAL

Ehrlich[34] adds to the discussion as to whether light urticaria is a genuine allergy or whether it is only a photodynamic phenomenon. Sulzberger and Baer[102] are quoted by Ehrlich as having obtained a positive passive transfer and ascribing the urticarial sensitivity as due to the presence of reagin in the blood stream. This is in support of the allergic theory for light sensitivity. Further discussion is given by this author to heighten the breach between those men of allergic inclination and those in support of the photodynamic theory. Ehrlich presents a case report of a patient having had itching and urticaria on exposure to sunlight over a period of ten years. Symptoms were less severe in winter than in summer, but were present in perennial fashion. A fluorescent lamp failed to reproduce the lesions, as did various other forms of artificial sunlight. Passive transfer studies in his patient were successful. Rubin et al[91] found that patients could markedly increase their tolerance to light with Pyribenzamine.

One of the most therapy-resistant conditions seen in the allergist's office is the

patient presenting himself with lesions characteristic of fungus sensitivity. No single method of therapy is successfully applicable to these patients and even when an apparent benefit has been found, subsequent remissions are the rule rather than the exception. The secondary lesions are usually of much greater severity and a source of much more discomfort than the primary focus. A large amount of fungus sensitivity is being seen today, and this may be stated to arise in the number or the type of infections that resulted from military service in various parts of the world. It is recognized that the secondary "id" lesions are of allergic origin and should respond to immunologic management. Sensitization is one of the primary factors in the development of these secondary lesions. These authors present thirty patients who have been followed over one year. Jaros and Kirsner[53] found associated allergy in 56.7 per cent of their patients. In an attempt to hyposensitize these patients, a dilute extract was chosen in order to avoid reaction symptoms in the most sensitive instances. If a dosage of more than 0.2 c.c. was used local necrosis was noted and best results were obtained with an amount of 0.1 c.c. at twice weekly intervals. Injections were given intradermally. After an average of 22.5 injections, results are reported as 93.3 per cent showing improvement with 40 per cent of these being classified as cured. This reviewer has used a plan somewhat similar to that described by these authors and has met with similar good results. Often the average patient with evidence of fungus sensitivity has been around to so many and varied types of therapy that he is reluctant to assume further time and expense in an apparently fruitless search. With such encouraging results as reported by Jaros and Kirsner, the outlook for some patients would seem much brighter.

Cohen and Kaufman[19] have found that, in four cases of penicillin urticaria, Procaine hydrochloride intravenously was successful in two patients. They point out the danger of possible sensitivity to the drug and warn against its use in indiscriminate fashion. The use of Procaine intravenously for the relief of the arthalgia and myalgia calls for a solution made up of 1 gram Procaine to 500 c.c. of physiologic saline. These writers report in detail the two instances in which Procaine was a failure under their management. In the discussion it is remarked that many forms of therapy were used without avail, and recovery was spontaneous and prolonged. No mention is made of the use of histamine intravenously, which preparation has met with almost astounding success in the relief of penicillin reactions of this type. An ampoule (1 c.c.) of histamine diphosphate of a strength 2.75 mg. (representing 1 mg. histamine base) added to 250 c.c. physiologic saline has relieved the majority of such reactions seen by this reviewer. It is felt that the administration of the histamine must be given in sufficient amount, strength and rate of flow to produce a mild flush. Prince[77] spoke on this at some length in the discussion of his paper in Oklahoma City.

A very interesting and worthwhile symposium on eczema-dermatitis has been published by Sulzberger, Tolmach, Hill, and Simon. The clinical picture of eczema is described by Sulzberger[103] as being characterized by erythema, edema, papules, vesiculation, oozing, weeping with subsequent thickening, lichenification, pigmentation and itching. He explains the different features and the reasons for such differences between so-called allergic eczema, numular eczema, seborrheic eczema and many others in which the morphologic changes are due to mechanisms other than immunologic. The recognition of a contact type of dermatitis indicates the prognosis and therapy. Therapy must consist of removal of contact or a reduction in the degree of contact with the determined causative agent. Local therapeutic measures must be appropriate, and no reliance can be placed upon the use of antihistaminic agents. Tolmach[106] feels that the allergic individual is not more easily sensitized than is the non-allergic worker. He explains the difference between "obvious" and "insidious" primary irritants. Simple protective measures will correct a dermatitis due to simple irritation, but true allergic dermatitis calls for a change in the oc-

cupation or the type of occupation for the employe. In infantile eczema, the removal of the suspected or proven offending food or environmental substance combined with proper dermatologic treatment will usually give a satisfactory end result. Environmental allergens are more important than foods in the older child. Hill[52] states that the probable reason for disappointment in the management of the older child's eczema is due to the lack of proper environmental control at the same time that the attempt is made to hyposensitize the patient to the offending environmental allergen which reaches the skin through inhalation or direct contact of some sort. Simon[98] has used scratch and intracutaneous tests, as well as patch, patch-scratch and inunction testing to obtain reactions to human dander in the sensitive patient with negative reactions in control cases. He finds that scales from certain patients possess the property of producing inflammatory reactions when applied to certain other patients with eczema. Twenty-four patients with eczema were tested with the scales of one patient which had proven to be exceedingly active and productive of reaction. The degree of positive reaction was higher in the use of these particular scales, forcing the conclusion that a small amount of allergen formed in the proper location of the skin produces a more marked effect than a greater amount of allergen obtained by ingestion or contact.

GASTROINTESTINAL

In a rather thorough review of the available literature, few articles in the past year have dealt specifically with the gastrointestinal tract. Those few, however, were of interest and should be included in this miscellaneous section. In three presented cases, the diagnosis of gastritis was made by gastroscopy. Afendoulis[3] found that the changes were essentially the same as those found in idiopathic or infectious gastritis with the exception that the onset is more sudden. The appearance of the membrane is one quite similar to other forms of gastric upset. Causative factors were determined to be drugs or food and observation was made following the ingestion of the substances. He feels that the reaction is due primarily to the direct action of histamine or similar substances upon the membrane. Chobot[17] presents a timely discussion and review of gastrointestinal allergy in a very interesting article. Most common adult symptoms are abdominal distress, burning and flatulence. In true allergy, the symptoms may be reproduced at will. Gastrointestinal allergy in children is usually evidenced by colic, pylorospasms, cyclic vomiting and vague abdominal pain. Whey, containing albumin, is the chief offending fraction of milk sensitivity. Pruritus ani, as an allergic state, has been mentioned by Pearson[72] and Whitney.[100] The effect of Benadryl upon gastric acidity is the presentation of Doran.[30] There seems to be some disagreement as to whether the antihistaminic drugs are in opposition to the production of gastric acid or whether the effect is one of neutralization if present in any degree. When first introduced, the drug was indicated to be suppressive to gastric acidity but since that time changes of opinion have been published and digested. Langley and Smyth[56] and Seibold[95] are other authors who have discussed food allergy and allergy of the gastrointestinal tract. The latter article was found to be well worth while and instructive in all phases. Rudolph and Sage[92] feel that there are two groups of patients with allergic problems referable to their digestive systems. The first group is comprised of those in whom the symptoms and reactions are exceedingly slight and may be easily overlooked or incorrectly diagnosed. The second group is made up of those patients with evident associated allergic states and in whom the digestive symptoms are recognizable as a part of the allergic affair. These authors draw upon their military experience and the cases that were seen during that time. It is their impression that the detailed history is of primary importance in the diagnosis of gastrointestinal allergy. In any event, thorough gastrointestinal studies must be

done. The presence or absence of skin test reactions is not the deciding factor alone in the diagnosis of an allergy affecting the digestive system. The accurate completion of a food diary is an essential feature that should not be overlooked for, by this means, the physician is able to determine the time and association of the symptoms with the causative, offending substances. Treatment when possible should be directed toward the elimination of the etiologic factor or factors with resultant hyposensitization and dietary routine. This reviewer has met with little or no success in the few attempts made to hyposensitize for foods. The elimination of the food has been found to be the only satisfactory means of successful therapy. Patient tolerance will determine whether he may use little, some or none of the causative substance without the production of symptoms. Nor has this reviewer been able to place a burden of responsibility for diagnostic accuracy upon the question of a positive or negative skin test in the search for the answer to gastrointestinal allergic conditions.

"Food allergy should be considered as a cause of fever when the physical examination and laboratory studies give no explanatory clues and especially when treatment based on positive findings gives no relief." Such is the opinion of Rowe.[90] He has presented a very complete case study in which the allergic fever was of the persistent type and was present daily for four and one-half months of hospitalization. The degree of allergy to the causative foods can only be determined by feeding tests after the complete elimination of excluded foods has shown a remission of symptoms. A maximum degree of allergy must be assumed until the symptoms, whatever they may be, have been relieved. The failure to consider allergy as a possible cause of otherwise unexplained elevations of temperature may account for needless surgical procedures or prolonged rest and hospitalization. The fever due to allergy is usually persistent but may be of the remittent type. It is wise to look for other manifestations of allergy which may accompany the elevation of temperature.

HEADACHE

Alvarez[4] is of the impression that migraine is a disease of the brain dependent upon inheritance for the condition. This predisposition is likely to remain throughout the life of the patient. The strain of everyday life and the psychic make-up of the individual will govern the severity and the frequency of the attacks. This author bases his findings upon a study of 500 cases, a great number of whom were of the female sex and who fit into a rather typical physical and mental plan. Because of the influence that such predisposition has, the added factor of allergy, hypertension and menstrual difficulties aggravate or initiate the migraine seizure. Alvarez feels that the most effective form of therapy consists of rest, reassurance, and the elimination of factors productive of tension and worry—all of which adds up to adequate psychotherapy. Symonds[105] and MacLaughlin[60] do not agree in all respects with the above presentation, but similarity can be found in their basic approach to the patient. Dixon[29] discusses the use of histamine in the diagnosis and treatment of headache. Boggs[14] also feels that intravenous histamine is of marked value if properly used and effectively administered in the treatment of the migraine attack. Goodman and Coonrad[43] gave 0.3 mg. histamine phosphate to 113 persons without the subjects knowing the nature of the medication. Twenty-one normal subjects failed to have a resultant headache from the subcutaneous histamine. Of thirty-four persons subject to headaches, twenty-two were histamine positive. Two of these, with a history of migraine, developed such severe attacks that measures other than adrenalin were necessitated. Following the use of 100 mg. Benadryl none of these positive twenty-two persons developed a headache. Further proof of such protection was displayed in the testing of fifty-four patients whose chief complaint was headache. Thirty-one of these developed their usual headache following the

injection of the histamine, but of these, eighteen were subsequently without headache after the protection afforded by 100 mg. Benadryl. These authors feel that the majority of periodic headaches are on a vascular basis. They recommend that adrenalin be used more frequently as a therapeutic measure for relief of headache. This is based upon their experience of finding the ability of the drug to relieve the headaches induced by the injected histamine solution. They found that Benadryl was 92.5 per cent effective in preventing headache from the same dosage which previously had produced definite, and, at times, alarming symptoms in their test patients. Schnitker and Schnitker[94] established the diagnoses of migraine in their patients with the sublingual administration of nitroglycerin. A dosage of 1/50 grain reproduced typical symptoms which were readily relieved with oxygen inhalation, ergotamine tartrate or carotid artery compression. The reaction from the administered drug is noted within two hours. Excellent relief of severe attacks was attributed to the use of dihydroergotamine tartrate by Blumenthal and Fakler.[12] The drug is given in a dosage of 1 mg. Toxic effects of the drug were noted in 26 per cent but were not of sufficient severity to warrant the discontinuation of the medication. Ergotamine tartrate was found to be the most effective medication in the hands of Friedman and Brenner.[41] More effective than any ergotamine derivative were combinations of the drug in association with caffeine or atropine given orally and rectally respectively.

Dees and Lowenbach[28] have presented the results of an electroencephalographic study of eighty-five allergic children. Occipital dysrhythmia was the outstanding feature of the results. It occurred in half of their allergic patients, and this was considered to be far higher than the expected finding in so-called normal children. The presence of a positive family history seems to have a definite correlation with this high incidence of occipital dysrhythmia. It was also noted that the longer the patient had had his allergic complaints the greater the tendency for the patient to show changes in his occipital pattern. Zeller[117] reports the third case of temporal arteritis in which eosinophile cells were a prominent feature of the cellular infiltrate. Excision of the arterial segments led to prompt and prolonged improvement and recovery. The condition was felt to be one of diffuse arteritis.

INFECTION

The role that infection or focus of infection plays in the initiation, aggravation or masking of the allergic symptoms in the average patient has always been an interesting feature of the specialty. The debate between the intrinsic and the extrinsic advocates will go on with much stimulation for many years and perhaps will never draw to a pleasant conclusion. It cannot be overlooked that infection does play a role in the production of many symptoms and probably many actual diseases which, through lack of proper recognition, are today included in another field. At least they are not considered as being primarily allergic in origin. Recent opinions emphasize the striking similarity between the acute joint manifestations of acute rheumatic fever and the joint involvement of serum sickness. The most important basis for such thought rests upon the delayed time for the appearance of the complaints after the infectious process has been noted or the serum has been administered. That the incidence of allergy is three times greater in rheumatic children than among non-rheumatic controls has been the findings of Rittwagen et al.[86] They were able to study one hundred rheumatic children and compare the findings with one hundred patients without the manifestations of the disease. Thirty-three per cent of the rheumatic group gave personal histories of having had hay fever, asthma, or food sensitivity. Thirty-one per cent had a positive family history of allergic disease. In the control group, only 8 per cent were sufferers of allergic disease, while 10 per cent were of allergic family background. Covelti[23] was able to produce in rats cardiac changes resembling those of rheumatic fever in human beings. This

was done by giving rats a series of injections containing killed streptococci and emulsions of rat heart or connective tissue. A possible pathogenesis for rheumatic fever is thus suggested by the author. The production of specific antibodies which react with the antigen in the connective tissue is the basis for this opinion. Cardiac enlargement and findings of pericarditis are part of the clinical picture described in McKinley's case report.[64] These clinical features were recognized twenty-three days after the injection of tetanus anti-toxin to a patient who had received routine immunization procedures while in service many years previously. Pleurisy with effusion, precordial friction rubs, and cardiac pain were all present during the reactive stage. All symptoms and signs rapidly disappeared within a week's time and the heart was found to be of normal size. Recovery from that time was uneventful and without consequence.

Baggenstoss, Bayley and Lindberg[10] feel that there is a definite underlying basis for allergy in Loeffler's syndrome. They report the presence of eosinophilic leukocytes in the pneumonic exudate in their patient, a woman with asthma of seven years' duration. Necrotizing arteritis and phlebitis, fibrosis and giant cells in the exudate and granulomatous lesions were other histologic presentations. No lesions resembling periarteritis nodosa could be found by Ayston and his co-workers[8] when they injected horse serum into rabbits. Their animals were given injections of serum over periods of thirty-three days with varying numbers of injections. Both gross and microscopic examination of the tissues failed to show any evidence of involvement. Placing sterile or infected silk sutures around the kidneys by Smith and Zeek[100] resulted in the production of typical lesions of periarteritis nodosa. The above measure resulted in a perinephritis with subsequent hypertension after one kidney had been removed from the animals. The lesions failed to develop if the hypertension was absent. They also found an absence of lesions when they injected horse serum into rabbits. They question the theory of hypersensitivity as a factor in periarteritis nodosa in view of their conclusion that hypertension was of primary importance. The etiology, pathology and clinical picture of periarteritis nodosa are reviewed by Miller and Daley.[66] Almost any organ may be involved but the kidney is the chief site of affection. An elevated eosinophile count usually occurs in less than 20 per cent. The symptoms, of course, are dependent upon the location of the pathology, and no clinical finding has been consistently present. Recovery may occur with little or no residual disability. Males are more commonly affected than are females, and the third decade is the age group of predeliction. Fibrinoid degeneration may be a common finding in many of these diseases—rheumatic fever, periarteritis nodosa, scleroderma, disseminated lupus erythematosus, serum sickness—but a common etiologic factor should not be considered. Baker and Pollack feel that there are sufficient essential differences between them to state that all are not on an allergic basis.[11] In lupus erythematosus, the vascular involvement is only one phase of connective tissue degeneration whereas periarteritis nodosa is primarily a vascular disease. Rheumatic fever can also be differentiated pathologically, because of the less extensive collagen degeneration and the Aschoff bodies. As above stated, periarteritis nodosa occurs more commonly in males, whereas lupus erythematosus is predominantly present in females. The rash of lupus erythematosus is not a reliable finding. Vascular lesions identical with those of periarteritis nodosa have been found by Bohrod in a case of tuberculous meningitis.[13] Inasmuch as the lesions were limited to the meninges, it has been suggested that they may have been allergic in origin, with the tuberculo-protein as the allergen and the blood vessels of the meninges as the hypersensitive reactive tissue. Tuberculin reactions were unchanged by the use of Pyribenzamine in five patients in the report by Guy.[47]

The production of a specific antibody by the exposure of tissues to an undigested foreign substance leads to the possibility that all types of hypersensitiveness are

upon a common basic principle. Scherago[93] uses the term bacterial allergy to include all types of hypersensitive reactions that may develop when the tissues are brought into contact with bacteria or their products. He discusses the five types of hypersensitivity and groups them as follows: anaphylaxis, atopy, tuberculin-type, Shwartzman, and heterophile toxicity. Peritonitis of allergic origin is the subject presented by Sison, Dionisio and Chavez.[99] Attacks of epigastric fullness, paroxysmal pain, nausea and vomiting, with ascites, eucocytosis and eosinophilia occurred in their patient in association with pregnancy on four occasions. Reproduction of the complaints with an injection of estrone and relief with epinephrine followed a careful clinical analysis. Peck, Siegal and Bergamini[73] believe that a delayed reaction to penicillin skin test is of clinical significance. They have classified penicillin reactions into four groups: serum-sickness-like reactions, contact, erythematovesicular eruptions at the site of previous fungus infections, and febrile reactions. Subcutaneous dosages of gradually increasing amounts of noncrystalline penicillin proved successful in overcoming the sensitivity to the drug in their presented case. Three times weekly, beginning with 400 units, injections of penicillin were given with each dosage being double of the previous one. When 20,000 units were given, the skin test reaction was small while a trichophytin test was markedly positive. Good clinical response without reaction was experienced with the administration of the drug in careful but highly adequate amounts. Negative reactions to penicillin were found twenty-seven days after the first negative skin test was determined.

HISTAMINE AND ANTIHISTAMINES

The available literature on this subject has been so voluminous, during the past few months, that no attempt will be made by this reviewer to make this section all-inclusive. In addition, the material is of sufficient importance to warrant a review dedicated to this subject without conflicting articles using required space. If one assumes that allergen-reagin interaction releases histamine, then the histamine theory for allergic reactions is sound. Histamine release may be the result of trauma as well as antigen-antibody reaction. Most antihistamine therapy is directed in one of two directions: a development of tolerance to histamine by a series of injections of histamine diphosphate or the administration of a drug that prevents the action of histamine upon the body tissues. It has been noted that the term "desensitization" should not be applied to the use of histaminic therapy. Feinberg[37] has stated that attempts to demonstrate the achievement of histamine tolerance have been inconclusive. He feels that the effectiveness of histamine in allergic conditions has been exaggerated and that desensitization to histamine is not the basis upon which beneficial results are obtained. To the best knowledge, the antihistaminic drugs are effective by competing with the liberated histamine in their attachment to the receptor cell. It should not be assumed that the flood of new drugs on the commercial market will extend to the patient any prolonged degree of protection nor will they be productive of any degree of immunization.

Curry[26] evaluates the use of histamine and histaminase. Histamine has been used as a diagnostic agent in the determination of gastric function. Its therapeutic value rests in its ability as a vasodialator. Histaminase has not lived up to the promise of the early reports. This same author found that the degree of bronchoconstriction was in close correlation with the dosage of histamine administered to patients with varying degree of asthma.[27] Measurement was by means of vital capacity. The results, however, varied with each individual patient and the severity of his allergic complaints. The bronchoconstriction was more rapid in onset following intravenous administration than by intramuscular injection. Control patients failed to respond significantly after either route had been used for the injection of the histamine. Rutin was found to protect guinea pigs sensitized to horse serum from anaphylactic shock but failed in protecting normal pigs from sufficient doses of

histamine.[81] The authors do not theorize as to the action of the rutin in affording its protection. Mayer is of the opinion that the "competitive theory"— antihistaminic substances compete with histamine in certain enzyme systems—is sound and is supported by the fact that relationship exists between the degree of histamine sensitivity and the patient response with antihistaminic preparations.[61] The following experiments were performed: sensitization of fifty-four guinea pigs with horse serum, twenty pigs sensitized with hog serum, and sensitization of guinea pigs with substances of low molecular weight. It was found that it was possible to prevent or suppress all manifestations of vascular sensitivity with moderate and nontoxic dosages of Pyribenzamine.

Aerosolization of antihistaminic drugs was effective in combating the bronchospasm from histamine aerosols in guinea pigs. Feinberg et al,[38] in a series of well-controlled experiments, found that the maximum duration of the protection was sixty minutes. Drugs varied in their ability to afford protection—one milligram Pyribenzamine per kilogram was the smallest amount required to give ten-minute protection to all animals and the duration was four to six hours; Histadyle or Thenylene in 3 milligram dosages gave protection for three and one-half hours while Decapryn protected the experimental animals for four hours in a dosage of 5 milligrams. Less of the drug was required when the route of administration was by aerosol than when intraperitoneal injection was made.

That the whealing capacity of the skin to histamine was unimpaired with histamine azoprotein has been determined by Dundy, Zohn and Chobot.[31] They studied twenty children and twenty adults, with six of the latter showing slight improvement under this form of therapy. These patients had migraine, angioedema and allergic rhinitis, respectively. They feel that their evidence does not bear out the therapeutic value nor the immunologic specificity of histamine azoprotein. Cohen and Friedman[21] found that the treatment of seasonal hay fever with this same product led to disappointment, but that the results in chronic urticaria were quite gratifying. Excretion of Benadryl and Pyribenzamine in the urine was studied by McGavack et al.[62] It was determined that 46 per cent of the Benadryl (a single test dose was 400 milligrams) was excreted within the first 24 hours and 20.1 per cent of the Pyribenzamine was recovered in the same duration. The blood levels were slower to rise with Pyribenzamine than with Benadryl, and the levels were maintained over a greater period of time. Iontophoresis was employed by Cohen et al to test twenty patients with various dilutions of histamine in order to determine whether there would be a change in response after the ingestion of Benadryl.[22] Their results demonstrated conclusively that there was a well-marked cutaneous antihistamine effect. The effect was rapid in its appearance. Arbesman, Cohen and Osgood[6] divided their clinic patients into two groups. The first section was treated specifically with pollen extracts with supportive therapy consisting of ephedrine and similar drugs. The second section were given placebo injections, and no medication was prescribed except Pyribenzamine. Clinic patients seemed to do better on Pyribenzamine than did private patients. They recognize the value of the antihistaminic drugs in the palliative treatment of seasonal hay fever, but their results have shown that the combined method of adequate hyposensitization plus Pyribenzamine was the eventual method of choice. The side effects of these drugs have been reported and one wonders if the so-called side effects may not be an actual part of the drug action. Wyndaham and Owens report a rather marked agranulocytosis following eight weeks' administration of Pyribenzamine.[166] Their patient, an elderly woman, recovered under penicillin therapy, but the neutrophilic percentage was seen to decrease from 55 per cent to 3 per cent. That the dosage of the drug is an integral part in the production of side effects was reported by Brown.[16] Drowsiness, nausea and insomnia were in direct proportion to the size of the dosage used to control possible after-effects of typhoid vaccine administration. One hundred and forty-four

patients were given 250 and 500 milligrams of Pyribenzamine, or were used as a control group. Acute labyrinthitis as a side effect with Benadryl medication has been reported by Swartz.[104] Six days after the institution of Benadryl therapy for hay fever, his patient presented symptoms which disappeared upon removal of the drug.

Eight of twenty-two patients with itching skin eruptions were reported to obtain a very satisfactory degree of relief with 2 per cent Benadryl ointment. But Perry[74] also reported that the same degree of relief was obtained with the ointment base without the antihistamine. It was assumed, therefore, that insufficient absorption of Benadryl was present for clinical effectiveness. Intramuscular aminophylline was used as an antipruritic agent and seven of seventeen patients experienced dramatic relief in a very short period of time.[36] The discomfort caused by the intramuscular injection was sufficient to bring forth the recommendation that such procedure not be used routinely for the relief of nonspecific itching dermatitis. Comparative studies are reported using Benadryl, Pyribenzamine, Hetramine, Neo-Antergan, 3015 R.P. and 3277 R.P. Winter[111] finds that the best degree of therapy can be obtained with the use of Neo-Antergan. The dosage of the trial antihistaminic drugs was varied to determine the smallest amount affording protection but the histamine was constant in aerosol administration. The toxicity index, with mice as the experimental animals, was highest for Pyribenzamine, though all toxic levels were far above the usual dosage given for routine therapeutic protection. In ten patients with bronchial asthma, Brown, Weiss and Maher[15] found that excellent relief was enjoyed by one patient with Decapryn. Moderate relief in four and no relief in the remaining five patients completed this group of clinic patients. Better results were noted in the treatment of seasonal hay fever—eighteen of twenty-six had excellent relief. The total results showed about 80 per cent of all groups of patients with varied allergic complaints to have been relieved with the drug. Side effects with Decapryn are roughly those noted with other members of this group of drugs. Drowsiness was experienced by about one patient in six, but the majority of these side effects were noted in the asthmatic group of patients to whom larger dosages of the drug were given. Patient preference for Decapryn was expressed by those persons who had previously been treated with other antihistaminic preparations. Antistine was studied in 100 patients.[40] In dosages ranging from 200 to 400 milligrams daily, some degree of symptomatic relief was seen in 59 per cent of patients with allergic rhinitis. Thirty-seven per cent of the asthmatic patients studied showed some degree of symptomatic improvement. In comparison with Pyribenzamine, Anistine was of less therapeutic value in those instances where the main complaints were of rhinitis type. The same finding was suggested when the two drugs were compared in urticarial lesions, asthma, and generalized pruritus. Antistine was less toxic and less likely to produce unpleasant side effects than was Pyribenzamine. Benadryl and Pyribenzamine were able to relieve over 80 per cent of patients suffering from pollen rhinitis or acute urticaria of varied origin. Loveless and Brown[59] found Benadryl to be somewhat more toxic and liable to cause drowsiness. As with all other members of this group of drugs, asthma remained quite resistant to the administration of the medication, even though the dosage was raised to what was considered to be adequate levels. No results whatever were noted in the relief of symptoms nor lesions of atopic eczema.

An ethlyenediamine derivative, Neohetramine, was studied by Waldbott and Borden,[114] with the finding that this drug was of relatively low toxicity. Two hundred seventy-nine patients were included in this study and were given 50 milligrams of the drug at four-hour intervals, as long as symptoms were present. A control group of 48 patients was given a placebo tablet containing ¼ grain of phenobarbitol. Ten per cent of the patients noted side effects from the trial drug with urticarial lesions and nasal complaints responding in best degree to the medication. Only 18 per cent of seventy-five asthmatic patients noted some degree of good relief.

The activity and lack of toxicity of Chlorothen and Bromothen, as reported by Litchfield and his associates,[58] has led to the marketing of a new antihistaminic preparation labeled Tagathen. Prolonged action, as compared with Pyribenzamine, was also noted. This reviewer has used this preparation during the hay fever season of 1948 and has found that beneficial results are experienced by patients who have found other members of this antihistaminic group to be too toxic for continued administration. Good results with Pyribenzamine in hay fever are also reported by Henderson and Rose[51] in a group of 138 patients. Again, the results were somewhat disappointing in the asthmatic group, inasmuch as only three of fifteen were improved, and aggravation of symptoms was noted in another three of this same classification. It was rather unusual, as the lack of similar reports will substantiate, to have one patient with migraine report excellent relief from the use of the drug. Neo-Antergan and Pyribenzamine have been clinically compared by Weiss and Howard.[108] They agree that hyposensitization therapy is more effective and reliable than are the drugs alone. The former drug was found to be more toxic and consequently less effective in the six groups of patients treated by these authors. Twenty-three of twenty-four cases of urticaria responded very well to the use of Pyribenzamine in a dosage of 100 to 400 milligrams daily.[71] Atopic dermatitis was somewhat less receptive to anticipated benefit, although the pruritus was relieved in about 50 per cent of the patients so classified. This drug was also of value in physical allergy. Pyribenzamine administration preceding skin testing was contributory toward the decrease of the size of the resultant wheal although the degree of response in this regard could not be correlated with the degree of relief reported by the patient. That the dosage of the antihistaminic compound is of primary importance in predicting the degree of relief to be anticipated has been propounded by Rose et al.[89] Linadryl was found to have an action similar to that of Benadryl in an effectiveness of about one-half the degree.[63] The drug was found to be most satisfactory in the relief of acute urticarial lesions and with decreasing effectiveness in chronic urticaria, perennial rhinitis, atopic eczema, bronchial asthma, hay fever and angioedema. Exertion as an aggravating factor in hay fever and asthma may be partially explained by Serafini in his finding of rising blood histamine a short time after physical exercise in some allergic patients.[97] No significant change in the blood level was noted in normal persons under similar conditions. With varied antihistaminic preparations symptomatic relief was obtained in eighty-four of 140 allergic patients.

Criep and Aaron have reported that Neohetramine is of lower toxicity than any of the other antihistaminic preparations.[24] Two hundred and forty-nine patients were used for this study and a very low percentage of side reactions was noted. Eighty-two per cent of seasonal hay fever patients were receptive of some degree of benefit. Thirty-seven per cent of asthmatic patients failed to obtain any improvement or relief with the drug, but the remaining 63 per cent had variable degrees of benefit. Arbesman[7] has compared the action of Neo-Antergan, Pyribenzamine, Hydryllin, Neohetramine, and Antistine in 291 patients. He reported the superior effectiveness of Pyribenzamine in allergic rhinitis, with Hydryllin being of greater benefit in the asthmatic group. This drug relieved 64 per cent of forty-eight patients with asthma. The question has always been in the mind of this reviewer whether such superiority might be aided by the aminophylline (though in recognized small dosage) contained in the preparation. It has been stated that the most potent and effective of these preparations are also the most active in their local anaesthetic properties.[44]

Benadryl was successful in the treatment of allergy to insulin. Leavitt and Gastineau[57] found that the generalized urticaria in one patient and the large local flares at the site of injection of the insulin in their second patient were well controlled and markedly reduced with 100 milligrams of Benadryl. Penicillin reactions are most common in patients who have had repeated courses of the drug. Pillsbury

and his co-workers report the effectivness of Benadryl in controlling some of the urticarial reactions from the drug.[75] They report fifteen cases of urticaria with the use of penicillin in eight hundred and twenty-four individuals under therapy for syphilis. Many of the reactions from the use of this drug fail to respond to any of the oral antihistaminic preparations. In almost the opposite view, Engelsher points out that the only relief with Benadryl or Pyribenzamine among his patients were those with acute urticaria.[35] The greatest majority of his patients with asthma or seasonal hay fever were unrelieved with these drugs, and in many instances the symptoms were definitely aggravated by the administration. Kieck[54] states that the use of antihistaminic drugs in the acute stage of contact dermatitis to plants and weeds has been of distinct benefit.

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PHYSICAL ALLERGY IN DERMATOLOGY

A Review of Recent Literature

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When W. W. Duke, the great pioneer of allergy, first used the term physical allergy, he meant allergic diseases caused by physical agents. Whether physical allergy differs basically from other types of allergy is still an open question. Formerly, the consensus was that physical allergy is not founded on an immunologic mechanism. In recent years, the study of light sensitivity especially has proved that some phenomena of physical allergy definitely are based on an immunologic mechanism. At present, it seems that various mechanisms, allergic and otherwise, are concerned in the manifestations of physical allergy.

The term "physical allergy" covers a variety of diseases which clinically resemble allergic diseases and which are caused more or less by physical agents. Physical factors play a role in many allergic conditions, other than skin diseases. This review, however, is restricted to physical allergy in dermatology.

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When we speak of physical agents, we usually mean the following:

1. Mechanical stimuli such as pressure and friction
2. Cold
3. Heat
4. Light

MECHANICAL URTICARIA

The most common form of mechanical physical allergy is urticaria factitia or dermographia. Severe whipping will produce a wheal in everybody. But some people are so sensitive to the touch that a slight stroking with a pencil will produce a wheal—a whitish raised area surrounded by redness. It is possible in those patients to write their name on the back of their skin by simply stroking them slightly. Hence, the name dermographia, which means skin writing. It is most likely that stroking of the skin or pressure releases some of the histamine of the skin, which in turn produces the phenomenon of mechanical urticaria.

Lewis[17] postulated that as a result of cell irritation caused by stroking the skin of a patient with dermographia, the interaction of the antigens and antibodies in a patient with urticaria, or physical irritants such as heat or cold in a sensitive person, a histamine-like substance ("H" substance) was released at that particular site and was responsible for the production of the wheal. There is good evidence that this "H" substance is actually histamine. Many observations tending to substantiate the histamine theory of wheal formation have been made. Rosenthal and Minard (1939) demonstrated that histamine could be released from isolated pieces of human skin by electrical stimulation. The role of histamine in anaphylaxis and allergy has recently been reviewed by Bram Rose.[16] Rose[22] as well as Nilzén[18] conclude, from repeated determinations of skin and blood histamine levels, that these levels remain remarkably constant in the same person. This was also found by Haworth and MacDonald. Rose showed that in a number of patients with dermographia, especially those showing a marked response, there is an increase in the blood histamine within five and fifteen minutes after stimulation. After twenty minutes and later, the blood histamine level often drops far below the normal value. Rose made similar observations on two cases of cold allergy and heat allergy. As yet there is no definite explanation of these phenomena. Formerly it was postulated that the histamine leaves the blood perhaps via the gastric secretion or by being absorbed by eosinophile cells in the wheal, or by some other excretion mechanism. Recently Rose[22] has advanced the theory that the increase of the blood histamine may stimulate the antihistaminic enzymes which may lead to a rapid neutralization of the histamine. Both Rose and Nilzén found that the histamine content of the blood of patients with urticaria or angioneurotic edema is at a very low level during an attack as compared to the level found during the quiescent stage. As far as mechanical urticaria is concerned, there is some good experimental evidence that it is caused by release of histamine. There is quite a variation in the histamine content of the skin in different persons, as shown in Table I. However, in a given person, the histamine content of the skin is quite constant.

TABLE I. HISTAMINE CONTENT OF SKIN AND BLOOD

Histamine content of skin		Histamine content of blood	
Author	8/gm.	Author	8/gm.
Nilzén	5 – 24	Rose & Browne	0.023 – 0.08
Pellerat & Murat	16 – 24	Nilzén	0.045 – 0.084

(8 = 0.001 mgm.)

Nilzén[18] studied the histamine content in wheals produced by mechanical stimulation in healthy individuals and compared it with the histamine content of adjacent normal skin. The results are summarized in Table II.

TABLE II. HISTAMINE CONTENT OF SKIN IN NORMAL INDIVIDUALS AFTER MECHANICAL STIMULATION

Time	Average values from Nilzén Normal skin 8/gm.	Wheal 8/gm.
2 min.	7.6	6.3
10 min.	11.5	6.2
25 min.	8.4	5.2
50 min.	11.6	11.3

There was not much difference in the histamine content of the wheal and normal skin after two minutes. But after ten and twenty-five minutes, the histamine content of the wheal dropped considerably below the values for the normal skin. After fifty minutes there was no longer any difference. These experiments indicate the release of histamine by mechanical stimulation. The same holds true for dermographia, as is evident from further studies of Nilzén, as summarized in Table III.

TABLE III. HISTAMINE CONTENT OF SKIN IN DERMOGRAPHIA AFTER MECHANICAL STIMULATION

Time	Normal skin 8/gm.	Wheal 8/gm.
2 min.	13.	10.3
5 min.	10.6	6.3
10 min.	16.	8.7

Urticaria factitia is different from ordinary urticaria. Many patients who suffer from dermographia do not have any signs of urticaria, and vice versa. Still there is probably some inter-relationship because the two conditions are frequently associated. The role of allergy in dermographism is still under discussion. Cazort[9] believes that positive passive transfer in dermographism is very rare. Psychosomatic aspects of dermographism are discussed by Dengrove.[10] He reports two cases in which psychologic factors seemed largely responsible. In both cases there are three factors to consider: (1) The constitutional background which reveals reacting skins in other members of the family; (2) emotional immaturity; and (3) dermographism associated with pruritus, with the onset linked to separation from supporting persons, in one case by death of the mother, and in the other by removal from a crew to which the patient was intimately attached.

URTICARIA FROM COLD

While most of us think that urticaria from cold is a rare affliction, Urbach and Gottlieb[28] state that the incidence of cold urticaria is relatively high, and that we fail to recognize it. No doubt the relation to cold may be more or less obvious. Not every exposure to cold elicits the urticaria. In some instances mechanical irritation must be added to the cold.

Cold urticaria, at least to some extent, also seems based on histamine release. As Pellerat and Murat[20] have shown, the histamine content of the skin decreases after freezing, thus indicating release of histamine by this process. A temporary increase of the blood histamine in patients with cold allergy fits in well with the histamine theory. At least for some cases of cold urticaria we may assume that under the influence of cold also some of the tissue histamine is released and produces the urticaria. However, it is well to remember that *it is not all histamine that wheals.* It would be a mistake to assume that all cases of urticaria from cold are based on a histamine basis. There are apparently several mechanisms possible. Rose[23] reported a case of cold allergy which apparently was not due to histamine.

What is the relationship between cold urticaria and true allergy? Some cases of cold urticaria give a definite impression that there is some real allergic hookup. Supporting this idea are the reports by Lewis and others of a positive passive transfer in some cases of cold allergy. What the allergen is, one cannot state at present. There are on record cases of cold sensitivity which were cured by the elimination

of focal infection or parasitic infestation. Urbach believed that many of these cases are due to functional disturbances in the vascular innervation. The antihistamines have been used successfully in urticaria from cold. Perry and Horton[21] found Pyribenzamine of some value in three cases of hypersensitiveness to cold.

URTICARIA FROM HEAT

Some of the considerations about cold urticaria or cold allergy apply also to hypersensitivity to heat. There are people who exhibit hypersensitivity to both cold and heat. Urbach and Gottlieb[28] stress the point that many cases diagnosed as cold allergy are, in fact, not due to cold at all but to the flush of heat which follows the exposure to cold. As in cold urticaria, hypersensitiveness to heat may produce a local contact urticaria as well as general symptoms brought on by a reflex mechanism, which includes besides the generalized urticaria other allergic or vascular manifestations such as asthma. There is another form of heat allergy which is somewhat different. It is brought out both by exposure to heat and emotional stress. Grant and his co-workers have termed it the heat and effort syndrome; Hopkins, Kesten, and Hazel[14] have confirmed the findings that these cases represent a hypersensitivity to acetylcholine. The urticaria in these cases frequently does not show the large blotches of ordinary urticaria, but innumerable small urticarial lesions. Furthermore, this form of heat allergy may not even produce urticaria but just produce a pruritus. This form of heat reaction is now called cholinergic urticaria. Although a rare condition, it was extremely difficult to deal with. Some of the antihistaminics counteract also acetylcholine, although this action is much less pronounced than their antihistaminic potency. Benadryl has given satisfactory results in a case.[12]

Sigel[26] studied twenty-two patients with urticaria caused by heat, exertion and excitement. All patients were American soldiers stationed in Japan. The patients with this type of urticaria constituted 2.2 per cent of all dermatologic cases seen. A sudden change of climate seemed to be of etiologic significance since most of the patients had been stationed in warm and hot climates before being moved into the temperate climate of Japan, where their first symptoms occurred. The eruption was characterized by pinhead-sized wheals, with or without erythema, and accompanied by urgent itching, prickling, and burning sensations. Symptoms were readily produced by vigorous exertion, any form of external heat or any form of excitement. There was no evidence of histamine sensitivity. Treatment in general was unsatisfactory. Burckhardt and Steigrad[6] present an interesting study about the effect of hot drinks on the temperature of the skin. Drinking of a glass of hot tea produced a marked increase of the temperature of the skin. The maximum was reached after four to twenty-two minutes. In order to produce this effect, the temperature of the tea had to be so high that the test person felt it as burning hot. According to the sensitivity of the test person, this meant a temperature between 42° and 56° centigrades. As similar effects were produced by drinking a glass of brandy or the eating of horse radish, the authors believe that this phenomenon is a reflex originating from the receptors of the mucous membrane. The mere presentation of a hot drink also was able to produce a reaction in the sense of Pavlov's conditioned reflex.

LIGHT SENSITIVITY

Physical allergy to sunlight is perhaps the most complicated and also the most interesting form of physical allergy. But not all cases of hypersensitiveness to sunlight are allergic in origin. For instance, there are chemicals which sensitize every skin to sunlight, the so-called photodynamic substances. The reader is referred to Blum's[3] book (1941). The photodynamic action of lime oil has been studied by Sams.[25] If people prepare a limeade and get the oil from the rind on their fingers while exposed to the sun, they all will react with a severe sunburn

followed by pigmentation and darkening of the skin. This reaction can be produced on any skin, providing the concentration of the extract and the exposure to light is strong enough. But frequently sensitivity to sunlight is on an allergic basis. Patients may become allergic to the oil of the lime rind and sunlight. In this case, a slight exposure is sufficient to produce a severe dermatitis.

Another example of photo-allergy, as this phenomenon is called, is light sensitivity to sulfonamides. Some sulfa drugs like sulfanilamide will sensitize everybody to the sunburn spectrum of the ultraviolet, and also to the long ultraviolet and to the visible light.[7] This is a phototoxic reaction and can be brought upon at will under experimental conditions. However, the concentration required in the skin to produce this reaction is so high that patients receiving sulfanilamide in customary dosage do not exhibit signs of this photosensitivity. But there exists also a photo-allergic sensitivity to sulfonamides. Once a person has become allergic to the combination of sulfonamide and light, much smaller amounts of sulfanilamide and less light is needed to produce symptoms. Burckhardt[7] reports five cases of photo-allergic contact eczemas from the use of sulfanilamide ointments. Patch tests with sulfanilamide alone were negative; but patch tests with the same ointments followed by irradiation produced a vesicular dermatitis. Histologically, these reactions presented intraepithelial, lymphocytic spongiosis. This reaction was elicited both by exposure to natural sun and to filtered mercury-arc radiation which eliminated wave length below 3,000 ångstrom units. Burckhardt has shown that the phototoxic, as well as the photo-allergic effect can also be produced by long ultraviolet rays, although the maximum absorption of sulfanilamide is within the range of short ultraviolet rays.

Urticaria solare is a rare condition which has attracted more attention during recent years. Beal[2] studied two cases of solar urticaria. Their range of sensitivity was found to be between 2,967 and 3,341 Å with a maximum sensitivity of 3,131 Å. This sensitivity could be passively transferred; positive reactions were elicited by exposing the sensitive sites to the active wave lengths. Reactions occurred within thirty minutes, and sites remained sensitive for several days. Negative results were obtained with normal control sera. The incidence of positive transfers could be increased by exposing large areas of the patient's body surface to ultraviolet light before withdrawing the blood for passive transfer studies. The serum lost most of its potency by storage at ice-box temperature for eight days. It was inactivated at 56° C. in one-half hour as well as by irradiation with ultraviolet light. The sensitizing factor did not dialize through a semipermeable membrane. Some protection against solar urticaria was afforded by an ointment containing 30 per cent G-Salt (sodium salt of 2-naphthol-6, 8-disulfonic acid) which absorbed the rays to which the patient was sensitive. Greater protection was afforded by the antihistaminic drugs which permitted gradually increasing exposure to ultraviolet light for therapeutic purposes. This produced an increased tolerance, limited to the exposed areas which might be attributed to pigmentation and/or thickening of the horny layer of the skin. Beal believes that this type of sensitivity may result from the formation of antibodies against a physiological radiation product in the skin. Another case of urticaria photogenica studied by means of a spectrograph is reported by Burckhardt.[8] The maximum of sunlight sensitivity also was between 2900 Å and 3350Å. But there was also a reaction in the range of the long wave ultraviolet at 3650Å. Passive transfer was positive and was elicited by the same wave length which caused the urticaria in the patient. Ehrlich[11] also reported a case of urticaria photogenica due to wave length shorter than 3700Å. Passive transfer was positive. His paper contains a review of the pertinent literature. Treatment of hypersensitivity to sunlight has been usually unsatisfactory. The antihistaminics have been a valuable addition, although not always helpful. The first successful report is from Tyson.[27] He reported prompt relief in a case of solar urticaria treated with benadryl. His

case was complicated by dysmenorrhea which, incidentally, was also controlled by Benadryl. In Burckhardt's[8] case Antergan lowered the erythema threshold of the patient and also prevented a clinical eruption. The sunburn protecting action of antihistaminics has been studied by Kurtin et al,[16] Borelli[4] and Baer et al,[1,5] Kurtin et al, were able to prevent the development of sunburn by preceding iontophoresis with Pyribenzamine. Baer and his associates[33,34] confirmed these findings. However, their investigations indicate that this effect is due to the "antihistaminic" action but to the physical properties of Pyribenzamine. This drug absorbs the active wave lengths causing sunburn and therefore prevents them from reaching the skin. The absorption curve of Pyribenzamine shows a high extinction peak in the zones producing ultraviolet erythema. Baer, Kline, and Rubin corroborated their theory by additional experiments. They were able to protect the skin from sunburn reaction by placing the Pyribenzamine solution in quartz cups between the skin and the source of light, thus excluding any chemical effect on the skin. Furthermore, Benadryl, which shows no absorption within the sunburn spectrum, showed only a slight diminution of the ultraviolet erythema. However, these experiments do not exclude the possibility that there may also be some other mechanism by which the "antihistaminics" act as protection against ultraviolet. Borelli[4] studied the effect of oral medication of the antihistaminic drug Dimetina (dimethyl aminoethyl benzylaniline) upon the ultraviolet reaction of the skin. In the majority of cases a rise of the threshold erythema was noted. Also an increase of the latent period and a diminution of the degree and duration of the erythema. The pigmentation was less severe only occasionally. However, the subjective symptoms such as burning and itching were missing, even if they had been present and were still existing in areas that were irradiated as a control on the preceding day. Borelli concludes from his studies that a great part of the so-called antihistaminic (anti-allergic) actions of these drugs is due to their anesthetic capacity.

Niacin amide given orally produced only a slight lowering of the ultraviolet threshold in normal persons according to Burckhardt.[8]

The sunburn protecting effect of para-aminobenzoic acid was studied by Rothman and Henningson.[24] Para-aminobenzoic acid has an absorption band which embraces all the sunburn rays. As it is essentially unchanged, even after intense irradiation, is non-toxic and non-irritating for human skin, non-staining and easily miscible with ointments and emulsions, it seems well suited as a sunburn protectant for local application. The authors used 15 per cent para-aminobenzoic acid in Ruggles' cream. The protective action against the light from a mercury lamp of a 15 per cent para-aminobenzoic acid ointment in 0.03 mm. layer thickness was 50 to 100 times greater than that of the plain base. Thirty-two individuals who had complained about great sensitivity to sunshine and who had repeatedly suffered from severe sunburn reported absolute protection when exposing themselves to natural sun light. However, when sunbaths on beaches are combined with swimming, the cream had to be reapplied each time the person left the water because it is easily washed off. The authors were also successful in protecting a patient with solar herpes simplex and another patient with chronic discoid lupus erythematosus who was very sensitive to sunlight.

However, darkening of freckles and solar urticaria were not prevented by this ointment. The action spectrum of these conditions is different from that of sunburn, as shown by Felsher, Rubin and Rothman.[13] Besides the sunburn spectrum of about 2,900 to 3,100 ångstrom units, the long wave ultraviolet between 3,000 and 4,300 ångstrom units with a maximum at 3,400 units, produces a tanning effect. This "darkening phenomenon" is an immediate effect of irradiation. Felsher, Rubin, and Rothman explain the seasonal color change of freckles as an effect of this long wave ultraviolet radiation which produces oxidation and spontaneous reduction of preformed melanin granules. The long wave ultraviolet darkening cannot be

increased beyond a certain maximum. This maximum obviously depends upon the genetically determined number, size, and density of melanin granules in the individual freckles. Sunburn protectants such as para-aminobenzoic acid and tannic acid, with absorption bands confined to the sunburn spectrum do not protect against the darkening of freckles. For this purpose, substances must be used which have a broad absorption band in the range between 3,000 and 4,600 angstrom units.

The actual sensitizers are still unknown in most cases of allergic light sensitivity. The viewpoint that there is no relation between the excreted porphyrins and sensitivity to light recently has been expressed again by Orbaneja and Mendoza.[19] These authors isolated the porphyrins from the urine and feces in cases of epidermolysis bullosa, xeroderma pigmentosum, lupus erythematosus, erythema multiforme, erythema solare, eczema solare and hydroa vacciniforme. There was no relation between the amount of excreted porphyrins and the sensitivity to light. Patients exhibiting a high degree of light sensitivity may excrete but little porphyrin, whereas patients with a high excretion of porphyrins may be only slightly sensitive to light. Niacin amide produced clinical improvement in several cases, which was followed by an increased excretion of porphyrins. Even healthy persons who had been exposed to intense sunning at high altitude on the following day excreted up to 760 gamma of porphyrins. On the other hand, as Brunsting and Mason[5] state, attempts to reproduce an eruption in the skin of porphyric individuals by exposing them to sun or artificial light have been, for the most part, unsuccessful.

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News Items

PLEASE GIVE THIS NOTICE YOUR IMMEDIATE ATTENTION

Members of the College desiring to present the results of clinical or laboratory research, must send manuscripts, or a 250 word summary, to the Chairman of the Program Committee, Dr. John H. Mitchell, 695 Bryden Road, Columbus, Ohio, before December 15, 1948. The other members of the Program Committee are: Dr. Leon Unger, Dr. Harold Abramson, Dr. Ralph Bowen, and Dr. Lawrence Halpin.

Seventy booths have been engaged for an industrial and scientific exhibit at the Palmer House for the fifth annual meeting of the College on April 14-17, 1949. Requests for these booths have been most encouraging.

All members of the Chicago Allergy Society, as well as the Chicago Medical Society, are cordially invited to register and attend. There is no registration fee, and an attendance of 1,000 registrants is anticipated.

* * *

Dr. F. W. Wittich was one of the guest speakers at the Fifty-Third Annual Meeting of the Utah State Medical Association on September 2-4 at Cedar City, Utah, where he presented two papers entitled, "The Importance of Allergic Diseases in Medicine and Their Basic Management" and "Emergency Treatment of Allergic Diseases." He also participated in the panel discussion on medicine.

Dr. Charles W. Bancroft of Wilmington, Delaware, presented a paper for Dr. Wittich in the latter's absence at the One Hundred and Fifty-Ninth Annual Session of the Medical Society of Delaware on September 14.

* * *

Dr. Maurice S. Fox announces the association of Dr. George T. Raper in the practice of Allergy and Dermatology, Suite 223 American Bank Building, Vincennes, Indiana.

* * *

The Thomas Clinic has announced its opening on September 1, at 2031 Monument Avenue, Richmond, Virginia, with practice limited to Allergy and Internal Medicine. The Clinic is continued by J. Warrick Thomas, M.D., formerly associated with the recent Graham-Thomas Clinic, and Joseph M. Hester, M.D., formerly of Bowman Gray Medical School and Baptist Hospital.

* * *

Dr. Jonathan Forman, president-elect of the College, recently talked to the Ohio Farm Bureau (Franklin County, Ohio) on "Creative Medicine and Rural Health." He also has contributed an article on local medical history to the volume honoring Dr. Max Neurberger on his 83rd birthday.

* * *

Doctor Forman had an article in the May issue of *The Ohio Magazine* entitled, "Health from the Ground Up."

In the current issue of *The Land,* quarterly publication of "Friends of the Land," Doctor Forman has an article entitled, "What the Doctors Can't Fix," dealing with a positive approach to health.

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THE AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY

Dr. Lyman D. Richards, president of the American Laryngological, Rhinological and Otological Society, Inc., Dr. M. Murray Peshkin of New York City and Dr.

NEWS ITEMS

Fred W. Wittich of Minneapolis were the guests of honor and presented papers at the annual meeting of the American Society of Ophthalmologic and Otolaryngologic Allergy at the Palmer House, Chicago, Illinois, October 8 and 9. This rapidly developing national allergy society now has eighty-six members and is an official member of the International Association of Allergists.

Dr. W. Byron Black, a member of the Board of Regents of the College, is president of this society and Dr. French K. Hansel is Director of the Hansel Foundation which was established February, 1947, and which has already conducted a very successful Instructional Course.

Program

Practical Aspects of Ophthalmologic and Otolaryngologic Allergy
(Under the Auspices of the Hansel Foundation)

Friday, October 8, 1948
Room 14, Palmer House, Chicago, Illinois

A.M.
8:00 Registration
9:00 "Diagnosis of Allergy from Otolaryngologic Standpoint"—French K. Hansel, M.D., St. Louis, Missouri
9:45 "Allergy History and Diagnosis"—Joseph W. Hampsey, M.D., Pittsburgh, Pa.
10:30 "Skin Testing"—W. Byron Black, M.D., Kansas City, Missouri
11:15 "Ocular Fatigue (Syndrome) from Food Allergies"—A. W. McAlester, III, M.D., Kansas City, Missouri (by invitation)

12:00 LUNCHEON

P.M.
2:00 "Pollen Survey"—O. C. Durham, Chief Botanist, Abbott Laboratories, Chicago, Illinois
3:00 "Prophylaxis"—Eugene L. Delacki, M.D., Chicago, Illinois
3:15 "Dust Therapy"—Rea E. Ashley, M.D., San Francisco, California
3:30 "Pollen Therapy"—Walter E. Owen, M.D., Peoria, Illinois
4:00 "Dietary Manipulation"—Aubrey G. Rawlins, M.D., San Francisco, California
4:30 "Indications for Surgery"—Kenneth L. Craft, M.D., Indianapolis, Indiana

Saturday, October 9, 1948
Crystal Room, Palmer House, Chicago, Illinois

A.M.
8:00 Registration
9:00 "Management of the Asthmatic Child"—M. Murray Peshkin, M.D., New York, New York
9:30 "Histaminic Cephalalgia"—French K. Hansel, M.D., St. Louis, Missouri
10:00 "The Significance of Mold Spores in Ophthalmologic and Otolaryngologic Allergy"—Fred W. Wittich, M.D., Minneapolis, Minnesota
10:30 "Allergic Manifestations of the Ear"—Hugh A. Kuhn, M.D., Hammond, Indiana
11:00 "Experience With Minute-Dose Dust Therapy"—George E. Shambaugh, M.D., Chicago, Illinois
11:30 "Allergy From the Ophthalmologist's Standpoint"—William D. Gill, M.D., San Antonio, Texas

12:00 LUNCHEON

P.M.
2:00 ROUND-TABLE DISCUSSION—French K. Hansel, M.D., Moderator
4:40 BUSINESS MEETING
6:00 COCKTAIL HOUR—Room Eleven
7:00 BANQUET—Crystal Room
"Otolaryngology: Yesterday, Today and Tomorrow"—Lyman Richards, M.D., Brookline, Massachusetts

NEWS ITEMS

The Asthmatic Children's Aid has presented a gift of $10,000 to the University of Illinois colleges of medicine and pharmacy for investigative work in allergy.

The gift was presented to the University on July 8, 1948, by Mrs. M. Morton Strassman, retiring president of the Asthmatic Children's Aid. It was received in behalf of the University by Dr. Earl R. Serles, dean of the college of pharmacy, and Dr. John B. Youmans, dean of the college of medicine.

The Asthmatic Children's Aid has now contributed almost $40,000 to the University of Illinois' Allergy Unit since it was established in November, 1944.

FOREIGN NEWS

The dean of the Medical School of the University of San Francisco Xavier, Sucre, Bolivia, has invited Dr. Guido Ruiz-Moreno to conduct an Intensive Instructional Course in Allergy at this university and to co-operate in establishing an allergy service. Dr. Ruiz-Moreno has also been elected an Honorary Fellow of the French Allergy Society. Dr. Pasteur Vallery-Radot is the president of this society.

* * *

We are pleased to acknowledge receiving Number 1 of Volume I, *Acta Allergologica* with the compliments of the editor, Dr. Ernst B. Salén of Stockholm, Sweden. *Acta Allergologica* is published by Einar Munksgaard of Copenhagen. The Associate Editors are Dr. Egon Bruun of Copenhagen and Dr. C. Juhlin-Dannfelt of Stockholm. Members of the Editorial Board are Doctors K. Baagøe, H. Bergstrand, P. Bonnevie, N. Danbolt, G. Dohlman, P. Frenckner, H. Haxthausen, S. Hellerström, E. Jarløv, W. Kerppola, M. Kobro, H. Malmros, Eggert Møller, U. Siirala, C. E. Sonck, Th. Thjötta, P. Blamoutier, J. Duchaine, F. J. Farrerons, W. Jadassohn, J. Liska, and U. Serafini.

The new journal contains 119 pages of investigative allergy. It is published by the Northern Society for Allergological Research, and will appear at irregular intervals, generally about one or two volumes a year. Four numbers will form a volume. The journal will publish original research work in the field of allergy, in English, French, or German, at the choice of the author.

The first issue contains an article on "Ètat actuel de la question des anti-histaminiques de synthese" (The Present Status of the Synthetic Antihistaminics) by Dr. B. N. Halpern; one on "Considérations sur le mécanisme de l'hypotension artèrille au cours du choc anaphylactique et histaminique chez le lapin," (Observations of the Mechanism of Arterial Hypotension during the Histamine Anaphylactic Shock in the Rabbit) by Pasteur Vallery-Radot, B. N. Halpern and G. Mauric. There is also an article on "Action préventive d'un antihistaminique dérivé de la thiodi-phénylamine sur l'oedème aigu du poumon expérimental," (The Preventive Action of an Antihistaminic Derived From Thiodi-Phenylamine on Acute Edema of the Experimental Lung) by B. N. Halpern, J. Hamburger and S. Cruchaud.

PROGRESS IN ALLERGY

(Continued from Page 623)

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BOOK REVIEWS

FUNDAMENTALS OF IMMUNOLOGY. Second Edition. By William C. Boyd, M.D. 519 pages. 50 illustrations, 66 Tables. Price $6.00. New York: Interscience Publishers, Inc., 1947.

This second edition of Fundamentals of Immunology has been completely revised and rewritten. The rapid advances in our knowledge of immunology are adequately treated in bringing the text up to date. The basic principles of immunology in this introductory volume make it invaluable to medical students, chemists, and biologists.

Those desiring to undertake investigations in the field of serology will find the book of assistance because of the special detailed emphasis on the subject.

There are ten chapters listed in the contents: Immunity and Immunology, Antibodies and Antibody Specificity, Antigens, Cell Antigens, Blood Groups, Antigen-Antibody Reactions, Complement and Complement Fixation, Anaphylaxis and Allergy, Allergy and Immunity (Bacteria, Viruses, Parasites), Practical Use of Immunity (Artificial and Naturally Acquired), Laboratory and Clinical Technic.

The binding is durable for laboratory use, and the print and paper stock are a credit to the publishers.

SKIN MANIFESTATIONS OF INTERNAL DISORDER (DERMADROMES). By Kurt Wiener, M.D. 690 pages, 400 illustrations, 6 color plates. Price $12.50. St. Louis: The C. V. Mosby Company, 1947.

The author states that a recent systematic presentation of skin manifestations of internal disorders does not exist, and he hopes to fill this gap with the present book. It seems to the reviewer that the author has accomplished this task exceedingly well. This ambitious compilation covers the whole field in forty-three chapters. An inkling of the extent of the work put into this book may be gained by the fact that over 3,000 references are quoted. This book is both an invaluable reference book for consultation, and, at the same time, with the individual chapters well arranged, makes interesting reading.

The book is meant primarily for the dermatologist and internist, and therefore would interest most allergists. It provides easy and accessible information about the various dermatoses which are connected with internal disorders, as well as those medical disorders which present, at some time or another, skin manifestations. The allergist may be interested especially in those chapters which deal with the pathogenesis of microbids, focal infection, skin manifestations of pyogenic systemic infections, lupus erythematosus, drug eruptions, relationship of skin lesions with endocrine glands, especially the female hormones, relationship to puberty, menstruation, pregnancy, menopause, disorders of the blood and blood-forming organs, and many others. This book contains a wealth of well-presented information, part of which would be difficult to find elsewhere.

This is a book that belongs in every medical library and constitutes a valuable addition to the allergist's library.